European Journal of Inflammation

Letter to the editor

European Journal of Inflammation
2016, Vol. 14(3) 200–205

DOI: 10.1177/1721727X16674219
eji.sagepub.com
SAGE

Ablative fractional laser improves treatment of actinic keratoses with Ingenol Mebutate

Steven Nisticò,[1,2] Mario Sannino,[1] Ester Del Duca,[1] Federica Tamburi,[3] Ugo Bottoni[2] and Giovanni Cannarozzo[1]

Abstract

Actinic keratoses (AK) are pre-neoplastic lesions related to an excessive ultraviolet exposure that represent an emerging issue in the area of skin diseases which undergo high risk for developing squamous cell carcinoma (SCC). In this open study, we tested the safety efficacy profile of sequential ablative laser and Ingenol Mebutate gel (IngMeb). Thirteen patients with a total of 99 lesions were selected for this open study. When multiple lesions on the same area were found, the treatment area was split in half. In one group, fractional CO2 laser microablative treatment was performed the day before three daily applications of IngMeb 150 lg/g; the other group received IngMeb without previous laser ablation. Fifty-six lesions were treated with laser and IngMeb and a total of 43 lesions in the second group were treated with IngMeb alone. Results at the 12-week follow-up visit showed that a clearance rate of 50/56 (89.2%) had been achieved. On the side that was not pre-treated with laser, 31 out of 43 lesions were cleared (72.1%). In our opinion, ablative fractional laser treatment could improve topical treatment of AKs, or provide a further therapeutic option for resistant patients.

Keywords

actinic keratosis, Ingenol Mebutate, laser-assisted drug delivery, laser treatment

Date received: 17 February 2016; accepted: 15 September 2016

Introduction

Actinic keratoses (AK) are pre-neoplastic lesions or intraepidermal squamous cell carcinomas (SCCs) related to an excessive ultraviolet exposure. AK may progress into invasive SCCs.[1,2]

The risk of progression of AK to SCC (invasive or in situ) is highly variable. The risk of developing SCC increases with the number of AKs, with a relative risk of 1% in individuals with five or fewer AKs compared to 20% among patients with more than 20 lesions.[3]

Compliance to therapy is considered a problem when trying to achieve complete resolution; furthermore, patients are often elderly and cannot undergo surgery. All available topical AK treatments are not long-lasting and the most commonly used, cryotherapy, may cause disturbing hypo- or hyper-pigmentation of the skin.[4–6]

Photodynamic therapy (PDT) is recommended in treatment with multiple AK lesions and field cancerization.[7] The cost of such therapy is reported be higher in real-life situations compared with that seen in clinical trials.[8]

Ingenol Mebutate (IngMeb) is a hydrophobic diterpene ester with topical chemotherapeutic

[1]Department of Systems Medicine, University of Rome, "Tor Vergata", Italy
[2]Department of Health Sciences, University of Catanzaro "Magna Græcia", Italy
[3]Unit of Dermatology, Complesso Integrato Columbus, Rome, Italy

Corresponding author:
Steven Nistico, Dermatologist, Associate Professor of Dermatology, University Magna Graecia, Catanzaro, Viale Europa, Germaneto (CZ), 88100 Catanzaro, Italy.
Email: steven.nistico@gmail.com

effects that has been reported as safe and effective for field-directed therapy of AKs with treatments for 3 consecutive days when located on the face and scalp and 2 consecutive days when located on the trunk and extremities.[9–11] It works in a double way via rapid lesion necrosis and via specific neutrophil-mediated, antibody-dependent cellular cytotoxicity. Treatment generally induces rapid destruction of lesions. The drug targets immunologically residual dysplastic keratinocytes. The clinical efficacy of IngMeb on AK has been confirmed by its effect on angiogenesis, stem cell activity, and cell proliferation in vivo in clinical trials.[12] Enhancing penetration of this molecule can result in better therapeutic modalities for AK.[13]

Microablation with fractional lasers can remove superficial epidermal layers of the skin. Devices can work and ablate precise epidermal targets without damaging surrounding skin. This is why laser-assisted drug delivery (LADD) can be considered a modern and precise way to favor a better penetration of topical active principles.

Pre-treatment of the epidermis with microablative fractional lasers has been shown to be a promising anti-cancer treatment, that increases the absorption of topical medications in the case of PDT, for example.[14,15]

Ablative fractional CO2 laser has been widely used in cosmetic and dermatological conditions as reported in different studies.[16,17]

In our opinion, ablative fractional CO2 laser treatment may ameliorate treatment results after IngMeb.

Materials and methods

Thirteen patients (9 men, 4 women; age range, 55–83 years) with AKs on the scalp, face, neck, and arms had a total of 99 lesions.

The study was approved from the local ethical committee at the University of Catanzaro (Italy). All participants gave informed, signed consent to participate in the study. Patients characteristics are summarized in Table 1.

When multiple lesions on the same area were found, the target area was divided in two (half side non-blinded randomization); one side underwent field ablative fractional CO2 laser treatment the day before field application of IngMeb 150 lg/g (daily, for 3 consecutive days on a 25 cm^2 area); the other side was treated with daily field application of 150 lg/g IngMeb for the same 3 days. Fifty-six lesions were treated with laser and IngMeb and a total of 43 lesions on the other side were treated with IngMeb alone. Ablative fractional CO2 laser was performed with the Smartxide2 C60 fractional CO2 laser system (Deka Mela, Calenzano, Italy) using the following settings: 10 Watt, HP Pulse, SmartTrack, 400 μm spacing.

Ablative fractional CO2 laser was lesion-directed towards individual AKs with treatment of the hyperkeratotic areas and the surrounding areas for a maximum of 25 cm^2.

Local skin reactions such as erythema and fine bleeding were reported immediately after laser treatment. Medication with ice cold gauzes and antibacterial cream (fucidic acid) was applied immediately after treatment.

Dermatoscopic (Dermlite, 3Gen Inc., CA, USA) and Multispectral analysis (Antera 3D, Miravex, Ireland) were performed before and after treatment at follow-up in order to assess the achieved results via evaluation of typical patterns.

Patients were then instructed to apply IngMeb gel daily for 3 days on the treated and surrounding area to cover a 5×5 cm area.

Follow-up visits were performed at 12 weeks with dermoscopical and multispectral analysis.

Lesions were counted at every visit.

Statistical analysis was performed using parametric procedures (t tests) which supplemented the analysis based on mean and standard deviation. The analysis of correlation performed referred to Pearson.

Results

All patients completed the treatment. Local skin reactions (LSR) such as erythema and sometimes vesicles, oozing, and crusts were reported 2–6 days after treatment and appeared similarly in the laser–IngMeb and IngMeb areas for all patients and were considered typical LSR to IngMeb treatment. The treatment therefore was considered safe.

At 12-week follow-up, AK clearances appeared to be very good (81/99 lesions cleared, 81.8%). On the side that underwent ablative laser treatment a clearance of 50/56 (89.2%) was achieved. On the side that was not treated with laser, 31 out of 43 lesions were cleared (72.1%). Thus, there were statistically significant differences in the groups (difference of 17.1%; $P < 0.001$).

Table 1. Patients included in the study.

Patient sex and age	Area	Area with laser pre-treatment, number of AK lesions before and after	Area without laser pre-treatment, number of AK lesions before and after	Local skin reactions, area with laser pre-treatment	Local skin reactions, area without laser pre-treatment
AL M 67	Face	4 B 0 A	4 B 1 A	†	*
BC M 72	Scalp	6 B 1 A	6 B 1 A	*	*
RC M 59	Scalp	7 B 2 A	7 B 1 A	†	*
UG M 77	Face	4 B 0 A	4 B 0 A	*	*
AG F 68	Neck	2 B 0 A	4 B 0 A	*	*
DC M 73	Scalp	7 B 0 A	7B 1A	‡	†
ER M 79	Scalp	4 B 2 A	4 B 1 A	*	*
AB M 64	Scalp	2 B 0 A	2 B 0 A	†	*
RQ F 55	Face	4 B 0 A	4 B 2 A	‡	*
ES M 55	Face	3 B 0 A	3 B 2 A	‡	*
JR F 58	Arms	1 B 0 A	1 B 0 A	†	†
WA M 83	Scalp	3 B 1 A	3 B 1A	*	*
RN M 77	Scalp	2 B 0 A	3 B 2 A	‡	‡

*Erythema.
†Erythema and vesicles.
‡Erythema, oozing vesicles, and crusting.
A, after treatment; B, baseline.

Five of 13 patients had a similar result on both sides (Table 1). Side effects were present. Erythema appeared in all cases treated. Seven patients experienced erythematous reaction in both sides treated (with or without laser pre-treatment therapy). Six of 13 patients (46.15%; P <0.001) experienced worse side effects in pre-treated skin if compared with skin treated with IngMeb alone. No signs of photodamage persisted after the end of the study.

Figure 1 shows a patient at T0 before the treatment

Figure 2 shows the comparison between a patient at T0, after the first treatment, and at 3-month follow-up.

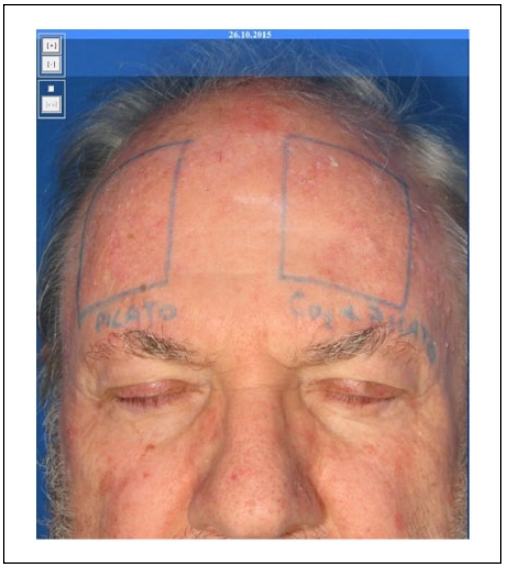

Figure 1. Patient before treatment (T0), right side Picato vs. left side Picato+ Co2 fractional laser.

Discussion and conclusions

Microablative fractional lasers have the capability to remove the upper layers of the epidermis, which

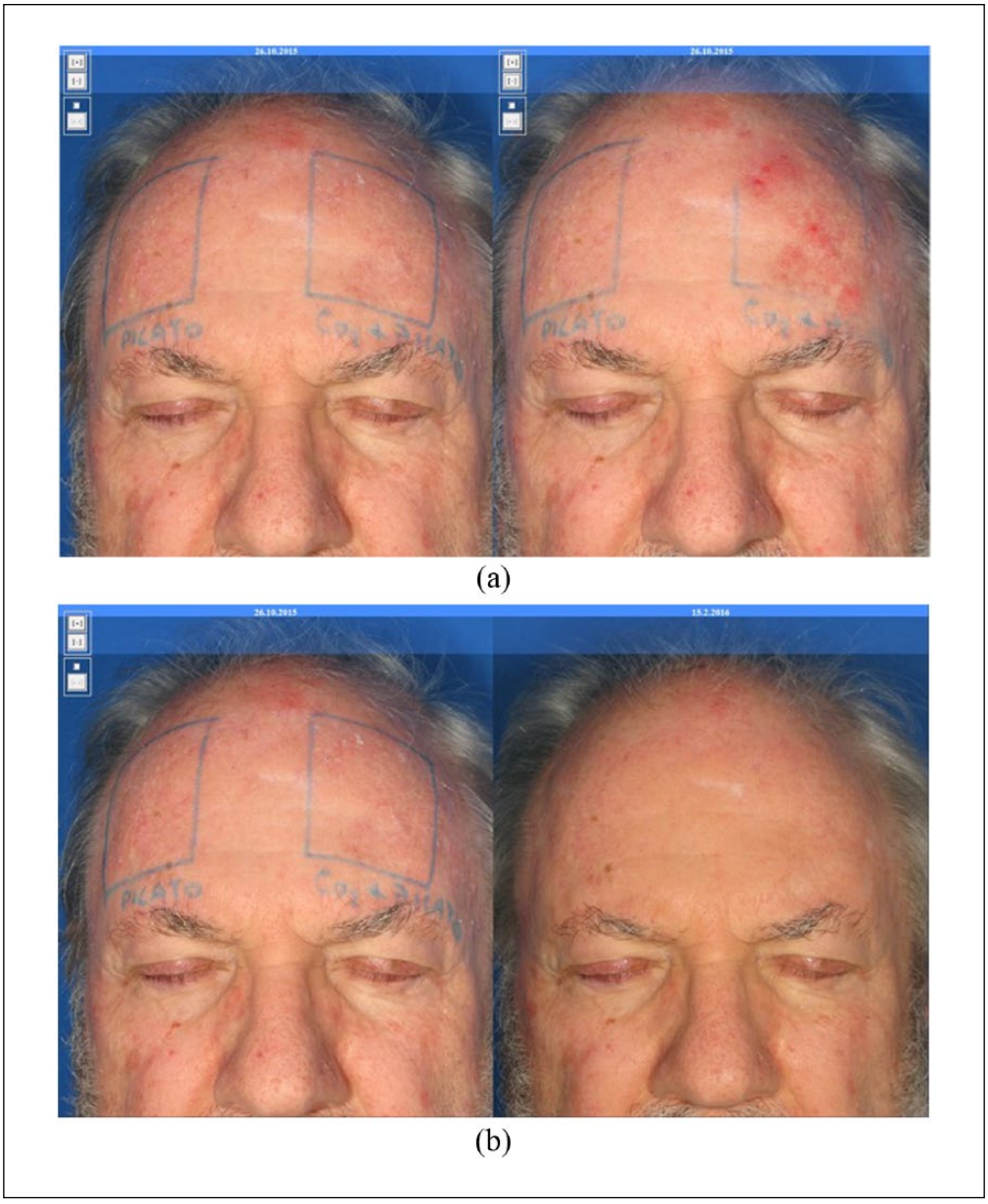

Figure 2. (a) (Left) patient before treatment (T0), (right) patient after the first treatment. (b) (Left) patient before treatment (T0), (right) patient at 3-month follow-up.

represents a physical barrier to the penetration of active principles through the skin. Therefore, drug delivery assisted by lasers or other energy devices has been recently proposed as a promising tool to allow an increased penetration of topically applied pharmacological active principles. For this reason, in our study we adopt a microablative fractional CO2 laser for colder and more delicate ablation thanks to the very low pulse emission times (H-Pulse).

This case series indicates that a combined laser–IngMeb treatment may be more effective versus conventional IngMeb topical treatment.

Results showed, on a total n of 99 lesions, an improvement of 89.2% on the side that had pre-laser treatment versus an improvement of 72.1% on the side that had IngMeb alone.

Dermal and epidermal inflammation was tolerable even if more pronounced after laser–IngMeb treatment in comparison to the counterpart.

Erythema appeared in all cases treated. Even though the side effects were worse with pre-treatment therapy with ablative laser, the procedure is well tolerated and side effects were moderate and did not need any special therapies of support.

Therefore, our study demonstrates that pre-treatment with ablative laser may enhance the immune-mediated reaction of the drug, and that reactions are tolerable and improve treatment outcome.

The reason for this, as other authors also suggest,[18] may be due to the reduction of the epidermal barrier, favoring drug absorption after laser exposure, enabling in this case, the diffusion of IngMeb in the lower layers of the epidermis and dermis, leading to a higher bio-availability. The increased effect of IngMeb on thicker lesions may therefore be explained.

Braun et al.,[19] in a case, report the effectiveness of laser-assisted treatment with IngMeb. This report shows that a previous application of an ablative Er:YAG laser enhances the inflammatory reaction of IngMeb in one patient with AKs.

Previously, some authors showed an increased transepidermal and dermal delivery of 5-fluorouracil (5-FU) after pre-treatment with conventional Er:YAG, conventional CO2, and QS Ruby lasers, respectively obtaining a 53–133-fold, a 36–41-fold, and a 5–10-fold increase with each system on animal models.[20]

Regarding human studies, some case series supported the efficacy of drug delivery assisted by lasers in the treatment of skin cancer, the ability of microablative pre-treatment with CO2 lasers to improve effectiveness of PDT with 5-ALA (aminolevulinic acid) and MAL (methyl-aminolevulinate).[21]

Our study, similar to a recent experience published by Karmisholt and Haedersdal[22] shows the results of laser–IngMeb treatment compared to IngMeb treatment alone on the same patient. The study reported efficacy and tolerable overall side effects on three patients at an 8-week follow-up with actinic lesion clearances enhanced on the side that underwent previous laser treatment in comparison to the IngMeb side in all three patients. Their results have been confirmed by our study that has a wider caustistic and a longer follow-up.

In conclusion, this case series may suggest a new procedure for improving the treatment of AKs or provide novel treatment of AKs for non-compliant or resistant patients.

Laser treatment can further improve the outcome of approved therapeutic modalities, In fact, IngMeb has been approved by the European Medicines Agency for its ability to improve the complete response rate of AK, for the short duration of treatment and the ease of self-application.[23] More clinical trials, with longer follow-up periods, should be performed on LADD especially for the treatment of pre-cancerous and cancerous skin lesions in order to establish their effective cost-efficacy profile.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Gupta AK, Paquet M, Villanueva E et al. (2012) Interventions for actinic keratoses. *Cochrane Database of Systematic Reviews* 12: CD004415.
2. Dodds A, Chia A and Shumack S (2014) Actinic keratosis: Rationale and management. *Dermatology and Therapy* 4: 11–31.
3. Patel RV, Frankel A and Goldenberg G (2011) An update on nonmelanoma skin cancer. *Journal of Clinical and Aesthetic Dermatology* 4: 20–27
4. de Berker D, McGregor JM and Hughes BR (2007) Guidelines for the management of actinic keratoses. *British Journal of Dermatology* 156: 222–230.
5. Dreno B, Amici JM, Basset-Seguin N et al. (2014) Management of actinic keratosis: A practical report and treatment algorithm from AKTeam expert clinicians. *Journal of the European Academy of Dermatology and Venereology* 28: 1141–1149.
6. Stockfleth E (2012) The paradigm shift in treating actinic keratosis: A comprehensive strategy. *Journal of Drugs in Dermatology* 11: 1462–1467.
7. Werner RN, Stockfleth E, Connolly SM et al. (2015) Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short version. *Journal of the European Academy of Dermatology and Venereology* 29: 2069–2079.
8. Ibrahim SF and Brown MD (2009) Actinic keratoses: A comprehensive update. *Journal of Clinical and Aesthetic Dermatology* 2: 43–48.
9. Lebwohl M, Swanson N, Anderson LL et al. (2012) Ingenol mebutate gel for actinic keratosis. *New England Journal of Medicine* 366: 1010– 1019.

10. Aditya S and Gupta S (2013) Ingenol mebutate: A novel topical drug for actinic keratosis. *Indian Dermatology Online Journal* 4: 246–249.
11. Martin G and Swanson N (2013) Clinical findings using ingenol mebutate gel to treat actinic keratoses. *Journal of the American Academy of Dermatology* 68 (Suppl. 1): S39–S48.
12. Bobyr I, Campanati A, Consales V et al. (2016) Ingenol mebutate in actinic keratosis: A clinical, videodermoscopic and immunohistochemical study. *Journal of the European Academy of Dermatology and Venereology*. DOI: 10.1111/jdv.13831.
13. Bobyr I, Campanati A, Consales V et al. (2016) Efficacy, safety and tolerability of field treatment of actinic keratosis with ingenol mebutate 0.015 % gel: A single center case series. *SpringerPlus* 5: 627.
14. Haak CS, Bhayana B, Farinelli WA et al. (2012) The impact of treatment density and molecular weight for fractional laser-assisted drug delivery. *Journal of Controlled Release* 163: 335–341.
15. Togsverd-Bo K, Haak CS, Thaysen-Petersen D et al. (2012) Intensified photodynamic therapy of actinic keratoses with fractional CO2 laser: A randomized clinical trial. *British Journal of Dermatology* 166: 1262–1269.
16. Cannarozzo G, Sannino M, Tamburi F et al. (2014) Deep pulse fractional CO2 laser combined with a radiofrequency system: Results of a case series. *Photomedicine and Laser Surgery* 32: 409–412.
17. Cannarozzo G, Sannino M, Tamburi F et al. (2015) Flash-lamp pulsed-dye laser treatment of keloids: Results of an observational study. *Photomedicine and Laser Surgery* 33: 274–277.
18. Micali G, Lacarrubba F and Nasca MR (2015) Reply to: "Laser assisted drug delivery: Enhanced response to ingenol mebutate after ablative fractional laser treatment". *Journal of the American Academy of Dermatology* 72: 365–366.
19. Braun SA, Hevezi P, Homey B et al. (2015) Laser-assisted drug delivery: Enhanced response to ingenol mebutate after ablative fractional laser treatment. *Journal of the American Academy of Dermatology* 72: 364–365.
20. Lee WR, Shen SC, Wang KH et al. (2002) The effect of laser treatment on skin to enhance and control transdermal delivery of 5-fluorouracil. *Journal of Pharmaceutical Sciences* 91: 1613–1626.
21. Haak CS, Togsverd-Bo K, Thaysen-Petersen D et al. (2015) Fractional laser-mediated photodynamic therapy of high-risk basal cell carcinomas: A randomized clinical trial. *British Journal of Dermatology* 172: 215–222.
22. Karmisholt KE and Haedersdal M (2016) Ablative fractional laser intensifies treatment outcome of scalp actinic keratoses with ingenol mebutate: a case report. *Journal of the European Academy of Dermatology and Venereology* 30: 854–855.
23. Tzogani K, Nagercoil N, Hemmings RJ et al. (2014) The European Medicines Agency approval of ingenol mebutate (Picato) for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults: Summary of the scientific assessment of the Committee for Medicinal Products for Human Use (CHMP). *European Journal of Dermatology* 24: 457–463.