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CLINICAL REPORT

IGF1 synthesis after CO_2 fractional laser resurfacing (FLR): New insights in the treatment of scalp actinic keratoses

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Abstract

Objectives: Actinic keratosis have a high risk of progression to a squamous cell carcinoma. Insulin-like growth factor 1 and its receptor play a relevant role in restoring repair of ultraviolet-induced cell damage. This pathway is reduced in patients older than 65 years. Ablative fractional laser resurfacing could normalize insulin-like growth factor 1 (IGF-1) secretion in elderly by recruiting new fibroblasts. The aim of the study is to evaluate restoration of IGF1 values by PCR in senescent fibroblasts after ablative fractional laser resurfacing.

Methods: We enrolled 30 male patients with multiple actinic keratosis on the scalp, equally divided into two mirror areas of up to 50 cm^2, treating only the right one. We performed one skin biopsy for each area 30 days after treatment. Real-time PCR in fibroblasts was performed to assess the change in IGF1. At baseline and after 6 months, in vivo reflectance confocal microscopy examination was performed in all patients.

Results: IGF1 values were increased in the treated side by about 60%. The right areas had fairly complete resolution of actinic keratosis at the last follow-up visit after 6 months with no appearance of new lesions. The mean number of actinic keratosis in the right area was reduced by more than 75% at four- and six-follow-up visits compared to the left area. The improvement in the right area was also evidenced by lower values of the mean AKASI (actinic keratosis area and severity index) score. Reflectance confocal microscopy showed a reduction of keratinocytic disarray and scales after treatment.

Discussion: Taken together, all the clinical, laboratory, and in vivo results of our study allowed us to confirm that ablative fractional laser resurfacing is a valuable tool for the treatment of actinic keratosis and cancerization field, both for the management of clinically evident lesions and for preventing the occurrence of squamous cell carcinoma.

KEYWORDS

actinic keratosis, cancerization field, insuline-like growth factor, laser, reflectance confocal microscopy

INTRODUCTION

Actinic keratosis (AKs) are the most common precancerous skin lesions, predominantly affecting older and fair-skinned people and localized in photo-exposed area, such as the scalp. Their prevalence has increased in recent decades, with a higher rate in warmer climate countries.[1] The risk of progression to a squamous cell carcinoma (SCC) is still unclear and varies from 0.1% to 20% and it is higher in the presence of multiple AKs.[2] Frequently, visible AKs are associated with adjacent subclinical lesions, which has led to the concept of cancerization field.[3] This is an area of skin

chronically photo-exposed with cumulative sun damage leading to appearance of clinical and subclinical lesions. Exposure of keratinocytes to ultraviolet (UV) radiation (mainly UVB), especially in the early years of life, leads to a dose-dependent accumulation of genome damage.[4,5] The aging process can cause morphological and physiological changes in the skin,[6] including a decrease in epidermal thickness,[7] epidermal cell turnover,[8] and the number of enzymatically active melanocytes,[9] all of which can reduce the ability of the epidermis to protect itself from the UV-induced DNA damage.[10,11] It has been validated that in patients over than 65 years, the inadequate response to UV-induced damage appears to be mainly due to an increased rate of senescent fibroblasts in the papillary dermis with overexpression of the onco-suppressor p53 inactivating protein (BP53).[12] This would lead to a failure to block cell proliferation of mutated clones and thus tumor progression.[12] Furthermore, we know that through the regulation of various intracellular signaling pathways that control cell proliferation, growth factors can play roles in cell biology. In particular, the transduction pathway of insulin-like growth factor 1 (IGF1) and its receptor (IGF-1R) in the skin is an excellent example of the interdependent relationship between fibroblasts in the papillary dermis and keratinocytes in the epidermis. Keratinocytes express the heterodimeric receptor IGF-1R, which is activated after the synthesis of IGF-1 by fibroblasts. Progressive aging of the dermal fibroblasts leads to a significant reduction in IGF-1 expression resulting in relative inactivity of IGF-1R in the epidermis. This reduces the ability to remove damaged neoplastic clones of keratinocytes and leads to an increased risk of developing non-melanoma skin cancers (NMSCs).[13,14] Management of AKs is a challenge of growing importance for dermatologists. Surgical and chemical treatments can be effective in treating precancerous lesions, although they can be extremely disfiguring and difficult for the patient to bear, as well as costly to the national health system. It is well known that lesion-directed therapies (such as cryotherapy, surgical courettage, and carbon dioxide [CO_2] fully-ablative laser) and field-directed approaches such as photodynamic therapy (PDT) and CO_2-fractional laser resurfacing (FXL) can be considered.[15] In recent years, this latter technique has been used for a comprehensive approach to damaged actinic area. The CO_2-FXL laser, with a wavelength of 10,600 nm, has a reduced risk of scarring compared with fully ablative lasers.[16] FXL, to date, has always been used for skin rejuvenation but less frequently for the treatment of skin cancers.[17] However, it has been studied as a treatment of AKs and reported a short-term reduction in the number of AKs.[18,19] Studied have also shown a lower risk of SCC in skin areas treated with FXL.[20] This phenomenon could be related to the re-epithelialization that occurs from follicular keratinocytes, which are relatively protected from sun damage.[20,21] In detail, it is possible to hypothesize that unirradiated epidermal stem cells from follicular keratinocytes may replace the damaged epidermis.[22,23] Considering all the hypotheses made so far, it is possible to speculate that fractional ablative therapies might be able to restore collagen expression by removing aged fibroblasts and recruiting new fibroblasts. This would lead to normalization of IGF-1 levels and restoration of a normal response to UV-induced cellular damage, with a reduction in carcinogenesis.[24] The purpose of our study is to evaluate, as primary endpoint, the increase in IGF1 synthesis by the scalp fibroblasts after CO_2-FXL in patients with multiple AKs. The secondary endpoint is to confirm the role of CO_2-FXL also as preventive tool for AKs by evaluating the reduction in number by clinical examination and reflectance confocal microscopy (RCM) before and after the treatment.

METHODS

Study design

We conducted a comparative, randomized, single-center study in the Unit of Dermatology, Siena University Hospital. The study was designed in accordance with the Declaration of Helsinki and subsequent amendments. We recruited 30 consecutive male patients aged ≥65-years with multiple AKs (grading 1 or 2) over the entire scalp, with a symmetrical distribution in two specular areas up to 50 cm^2 obtained by dividing them with an imaginary sagittal line (at least three AKs in each area). The diagnosis of AKs was based on clinical and dermoscopical analysis. Exclusion criteria were diabetes, immunosuppression, use of topical steroids on the scalp 2 weeks before recruitment, contra-indications for CO_2-FXL such as skin infection in the treated area and photosensitive skin diseases. All patients gave informed signed consent. At baseline (T0) patients started CO_2-FXL treatment only on the right scalp area once every 21 days for three consecutive times. All treatments were performed under local anesthesia using lidocaine 20% + tetracaine 5% cream in occlusion for 40 min. We used the Deka SmartXide2® CO_2-FXL laser (Deka). The defined parameters were 20 W, microbeam diameter of 300 mm, spot spacing of 55 mm, and dwell time of 700 ms. Prophylactic therapy with acyclovir 400 mg one tablet twice daily for 2 days before and 7 days after treatment was prescribed. All patients were recommended to wear a hat for the next 15 days outside the house. The left side of the scalp was not treated. Hyperkeratotic plaques were mechanically debrided in both hemispheres before each treatment. Local skin reaction (LSR) was evaluated for each patient, considering erythema, scales, crusting, swelling, vesicles/pustules, and erosion/ulceration after each treatment. All these parameters were reported from 0 (no reaction) to 4 (skin reaction extending beyond the treated area).[25] The composite LSR score (0–24) was then calculated. At T1, 30 days after the last treatment, all patients underwent two skin biopsies, one for each area, using a 6 mm diameter punch, after defying landmarks 2 cm from the midline and 5 cm from the anterior and posterior pole of the scalp. Patients underwent two

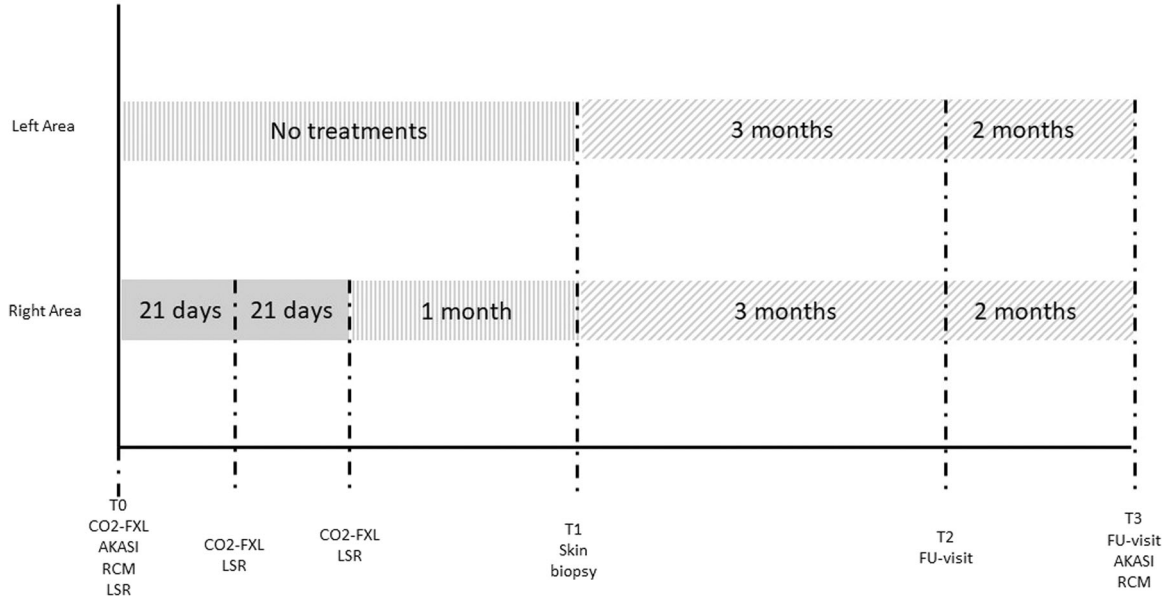

FIGURE 1 Study design. At baseline (T0) we performed AKASI, RCM, and CO_2-FXL (one treatment every 21 days). Local skin reaction (LSR) was assessed for each treatment. After 1 month from the last treatment (T1) we performed two skin biopsies (one for each scalp area). The first follow-up visit was 4 months after the last treatment (T2) and the second after 6 months (T3). At T3 we performed AKASI and RCM. AKASI, actinic keratosis area and severity index; RCM, reflectance confocal microscopy.

follow-up visits at 4 months (T2) and 6 months (T3) after treatment. All subjects were evaluated for the number of AKs and actinic keratosis area and severity index (AKASI) score[26] at baseline and T3. At T0 and T3, in vivo RCM (Mavig-Vivascope® 1500-3000) was performed in all patients to reveal any changes in keratinocytes. We decided to use RCM because the ability to acquire patient data and images quickly and inexpensively has become critically important to implement models for clinical decision making[27] and, in this case, to evaluate whether to perform a new posttreatment biopsy. At T0 we used the same points defined and used for biopsy. At T3, the images were acquired moving laterally by 1 cm to minimize the artifacts due to scar fibrosis. Two stacks (vertical pile of images) and one cube (vertical pile of mosaic images of 8 mm × 8 mm) were acquired for each site. The images were evaluated in blind by one expert (E.C.). We evaluated all criteria already defined in the literature as diagnostic for AKs, such as the presence of hyperkeratosis, parakeratosis, and scales in the stratum corneum, atypical honeycomb pattern of the epidermis, single dyskeratotic cells in the epidermis and solar elastosis and arrangement of collagen fibers in the dermis.[28] The study design is reported in Figure 1.

IGF1 dosage

After manual fragmentation, the surgical samples obtained by skin biopsy were divided into two 25-cm^2 flasks, added with DMEM® (high-glucose medium without L-glutamine added with penicillin, streptomycin, and fetal bovine serum at 10%) and placed in a thermostat at 37°C for 30 days for culture. Fibroblasts obtained from the first incubation (Figure 2) were then re-seeded for 7 days. IGF1 synthesis was evaluated by real-time PCR (RT-PCR). Since this method does not discriminate the starting parameters and it is impossible to use a value of 0, we defined an IGF1value of 1 for the left untreated area, which was considered as control. For the treated area, we obtained two values for each patient, one for each of the two flasks. To minimize bias from data, we calculated an arithmetic mean value (Table 1).

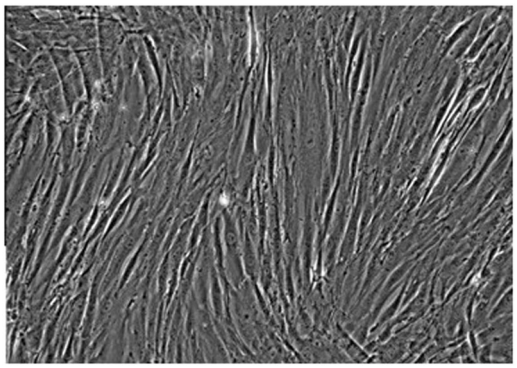

FIGURE 2 First fibroblast culture. Image obtained with Zeiss Id3 biocular invertoscope at 10×.

Statistical analysis

Quantitative variables were summarized with mean ± SD and minimum–maximum interval. The normality

hypothesis of the distribution was evaluated with the Kolmogorov–Smirnov test and the homoscedasticity of variances between right- and left-side measurements and between before- and after-treatment measurement with Bartlett's test. It was tested if IGF1 had a mean value greater than 1 with one-side *t*-test (alternative hypothesis mean>1). AKASI index was compared between left and right sides and before and after the treatment with the Wilcoxon test due to normal distribution.

TABLE 1 PCR-IGF1 values of the patients enrolled.

	Value LA	Value RA
1	1	1.33
2	1	2.08
3	1	1.33
4	1	2.01
5	1	1.56
6	1	1.43
7	1	2.24
8	1	1.67
9	1	1.67
10	1	1.94
11	1	1.31
12	1	1.13
13	1	1.81
14	1	1.61
15	1	2.03
16	1	1.51
17	1	1.28
18	1	1.53
19	1	1.21
20	1	1.24
21	1	1.08
22	1	1.13
23	1	1.69
24	1	1.29
25	1	1.41
26	1	1.32
27	1	1.46
28	1	1.87
29	1	1.85
30	1	1.06
Mean	1	1.54 ± 0.32

Abbreviations: LA, left area; RA, right area.

RESULTS

We included 30 male patients with a mean age of 76.5 ± 3.73 years. Analysis of the results showed an increase in IGF1 synthesis after CO_2-FXL. We could observe significantly higher values of IGF1 in the treated side compared to the left side of about 30%–200% for the individual evaluations (mean of 60%) ($p < 0.001$) (Table 1 and Figure 3). Compared with baseline, the right-treated areas had fairly complete resolution of AKs at T3, with no appearance of new AKs (Figure 4). The mean number of clinically visible AKs in the right area (RA) versus left area (LA) was 6.8 versus 6.8 at T0, 1.9 versus 6.8 at T1, 1.6 versus 7.2 at T2 and 1.6 versus 7.4 at T3 (Figure 5). All the results showed that 3-session laser therapy significantly reduced the number of lesions ($p < 0.001$). The mean AKASI in the RA compared with the LA was 3.25 ± 0.56 versus 3.04 ± 0.57 at T0 ($p = 0.16$) and 1.29 ± 0.44 versus 3.07 ± 0.58 at T3 ($p < 0.001$), highlighting a reduction of more than 75% (Table 2 and Figure 6). RCM showed clear-cut signs of AKs in both areas at T0. In detail, hyperkeratosis with an atypical honeycomb pattern of the epidermis, which partially involved the stratum granulosum, and areas of solar elastosis and fragmented collagen fibers in the dermis could be observed (Figure 7). Keratinocytic disarray was reported in all patients (100%), followed by inflammation (22 patients, 73%), parakeratosis (18 patients, 60%), and scales (11 patients, 37%). At T3, the RA appeared to have more compact collagen fibers and a regular honeycomb pattern of the epidermis (Figure 8). In addition, keratinocytic disarray could be found in four patients (13%) and scales in three patients (10%), while no other RCM signs of AKs were present. In the untreated area, images acquired in

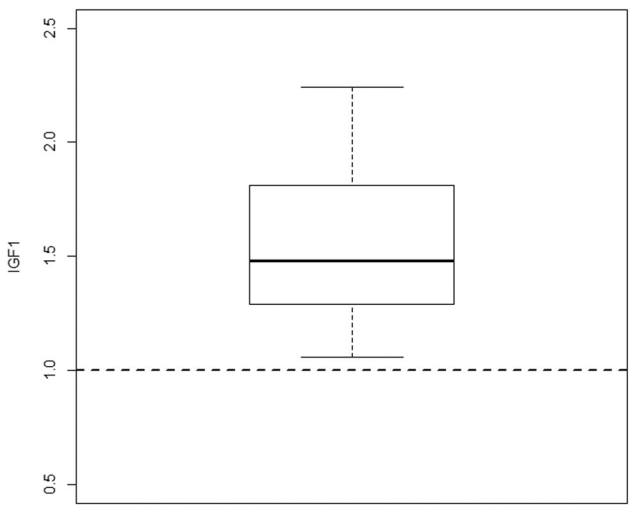

FIGURE 3 Box-plot showing IGF1 PCR values. The dotted line corresponds to the left untreated area with a conventional value of 1. The box corresponding to the right side treated with FXL shows a mean value of 1.54 (black line) with a maximum value of 2.24 and a minimum value of 1.06 (dotted bars). IGF1, insulin-like growth factor 1.

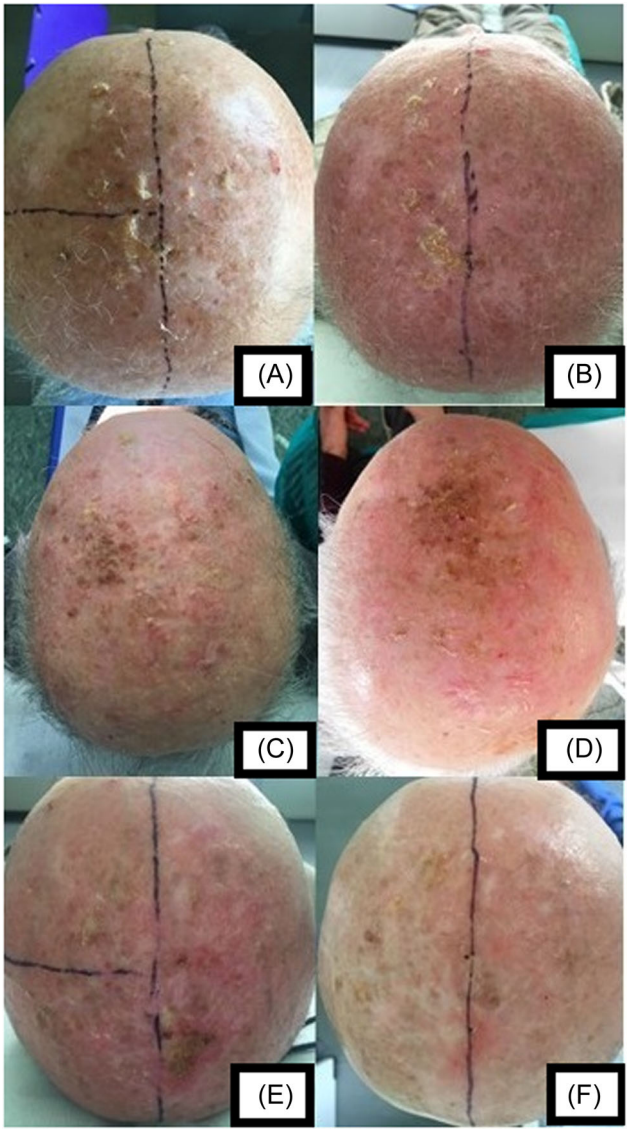

FIGURE 4 Patients before treatment (A, C, E) and follow-up visit at 6 months (B, D, F). Quite complete resolution on actinic keratosis in the right area of the scalp in the follow-up visit with few recurrences if compared with the left area.

RCM showed signs that were percentage superimposed on those shown at T0, with slight worsening in eight patients (27%). The mean LSR score was 15.7 after first treatment, 11.4 after second, and 7.8 after third (Figure 9). None of the patients developed skin infections. No pain was reported during treatment. In no patients did it become necessary to postpone or cancel the course of treatment. No severe adverse events occurred in our patients.

DISCUSSION

The study conducted in our hospital evaluated the quantitative synthesis of IGF1 by fibroblasts of the papillary dermis after CO2-FXL. In 2013, Spandau et al. treated 35 patients ≥65 years old in a 5 cm × 5 cm area of skin protected from photo-exposure (buttocks) with dermabrasion. After 3 months, the subjects were treated with UVB radiation (350 J/m^2) on the area previously subjected to dermabrasion and on a untreated area of equal size on the contralateral buttocks. Twenty-four hours after irradiation, subjects underwent two biopsies, one for each treated area. The study showed an increased IGF-1 mRNA levels in the area undergoing dermabrasion with coexisting reduction in aged fibroblasts.[29] We know that dermabrasion with removal of the entire epidermal layer and the superficial papillary dermis results in significant morbidity and a long recovery period. In addition, dermabrasion can cause scarring and long-term pigmentary changes.[29] Compared with dermabrasion, CO_2-FXL avoids both of these drawbacks with fewer adverse effects and better cosmetic result.[30] In addition, the absence of scarring after FXL could undoubtedly increase the compliance of patients who, due to chronic actinic damage in the context of the cancer field, often undergo multiple surgeries for NMSCs and numerous long-term topical therapies.[31] FXL has previously been shown to be effective in treating AKs of the face, scalp, and forearm, alone and especially in combination with PDT.[32,33] The concept of FXL as a drug delivery technique to overcome skin barrier has been reported in many clinical protocols.[34,35] When combined with other therapies, FXL greatly increased photosensitizer release in the epidermis and superficial dermis with shorter incubation times.[36,37] As monotherapy, the mean percent clearance of AKs after FXL treatment was 66.7% at 3–6 months follow-up visit, higher than diclofenac and placebo.[38] Two studies evaluated full-field resurfacing with CO_2,[39,40] one of which reported significantly higher percent clearance (92% at 3 months).[39] Our study aimed to confirm the results already reported but analyzing a sun-exposed area (scalp) instead of a sun-protected one (buttocks) and by preferring CO_2-FXL to dermabrasion in an area larger than 25 cm^2. We decided to exclude diabetic patients because IGF-1 and insulin have very similar molecular structures and high concentrations of insulin could activate IGF-1R. We hypothesized that in diabetic patients treated with exogenous systemic insulin, high hormone levels may compensate for an aging-dependent decline of IGF-1 in the skin by inadvertently maintaining the activation of IGF-1R despite reduced levels of fibroblastic IGF-1.[41] Analysing our results, we found a marked increase in IGF1 production in the treated area, confirming what has already been shown in the literature. Our data showed that the value was increased by about 60% compared with the untreated area, thus placing great expectations on FXL in restoring the proper response to UV-induced damage by reactivating senescent fibroblasts in the dermis. These findings shed new light on the effective role of FXL, especially as a preventive therapy for AKs. By inducing apoptosis of

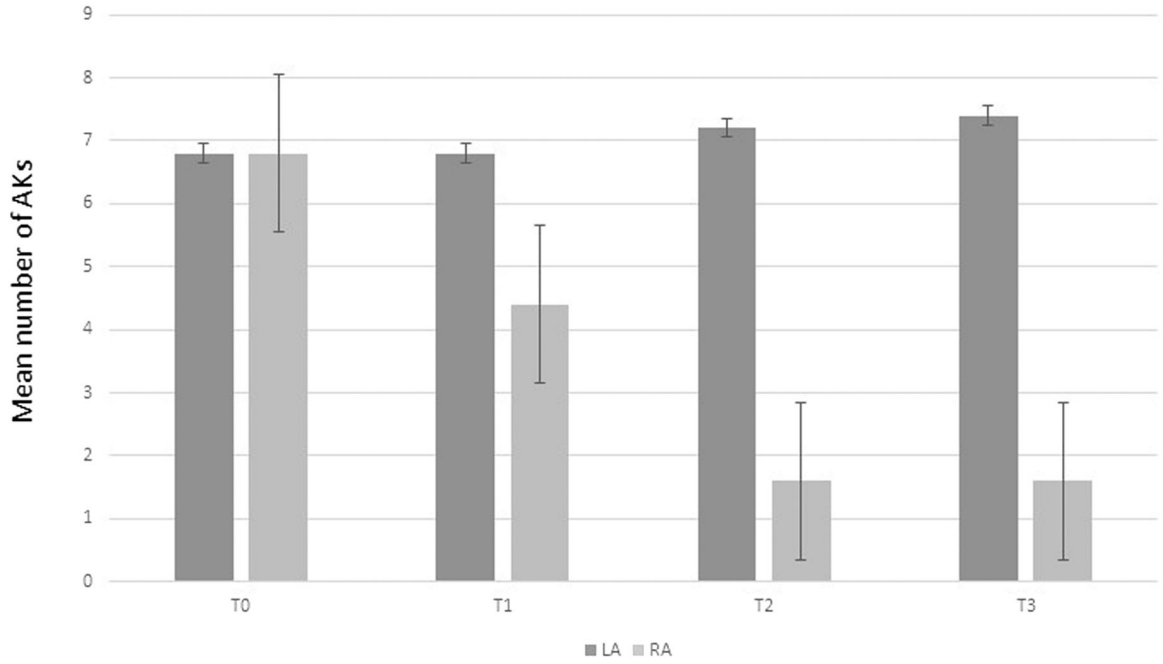

FIGURE 5 The effect of FXL on the improvement of actinic keratosis. Treatment course reduced the number and severity of lesions. Mean number of clinically visible actinic keratosis (AKs) in the right area (RA) (light gray) versus left area (LA) (dark gray) at T0 (6.8 vs. 6.8), T1 (1.9 vs. 6.8), T2 (1.6 vs. 7.2), and T3 (1.6 vs. 7.4).

TABLE 2 AKASI score: Values ported for single area and single patient before (T0) and after 6 months from the treatment (T3) and average value (AV).

Patient	AKASI right area T0	AKASI left area T0	AKASI right area T3	AKASI left area T3	Percentage variation RA T0 versus T3
1	2.8	2.6	1.2	2.6	57.1%
2	4.2	3.8	2.2	4.2	47.6%
3	3.4	3.2	1.2	3.2	64.7%
4	3.2	3.2	0.8	3.4	75.0%
5	2.8	2.6	1.6	2.6	42.9%
6	3.6	3.6	2.2	3.6	38.9%
7	3.2	3.2	1.2	3.2	62.5%
8	4.0	3.8	1.8	3.8	55.0%
9	3.2	3.4	1.4	3.4	56.3%
10	2.8	2.8	1.2	2.8	57.1%
11	2.8	3.2	1.2	3.2	57.1%
12	3.2	2.8	1.4	2.8	56.3%
13	3.6	3.2	1.6	3.2	55.6%
14	4.2	3.8	1.2	3.6	71.4%
15	3.8	3.6	1.2	3.4	68.4%
16	3.2	3.2	1.4	3.6	56.3%
17	2.6	3.6	0.8	3.6	69.2%
18	2.2	1.8	0.6	1.8	72.7%

(Continues)

TABLE 2 (Continued)

Patient	AKASI right area T0	AKASI left area T0	AKASI right area T3	AKASI left area T3	Percentage variation RA T0 versus T3
19	2.8	2.4	1.2	2.4	57.1%
20	3.4	3.2	1.4	3.2	58.8%
21	3.8	2.4	0.8	2.8	78.9%
22	4.2	3.8	2.4	3.8	42.9%
23	2.8	2.4	1.2	2.4	57.1%
24	3.2	3.2	0.8	3.2	75.0%
25	3.4	3.2	1.2	3.2	64.7%
24	2.6	2.4	0.6	2.4	76.9%
27	4.2	3.8	1.4	3.8	66.7%
28	2.8	2.4	1.2	2.4	57.1%
29	2.6	2.2	1.4	2.2	46.2%
30	2.8	2.4	0.8	2.4	71.4%
Mean ± SD	3.25 ± 0.56	3.04 ± 0.57	1.29 ± 0.44	3.07 ± 0.58	60.6% ± 10.6

Note: In the last column a percentage variation in RA from T0 to T3.
Abbreviation: AKASI, actinic keratosis area and severity index.

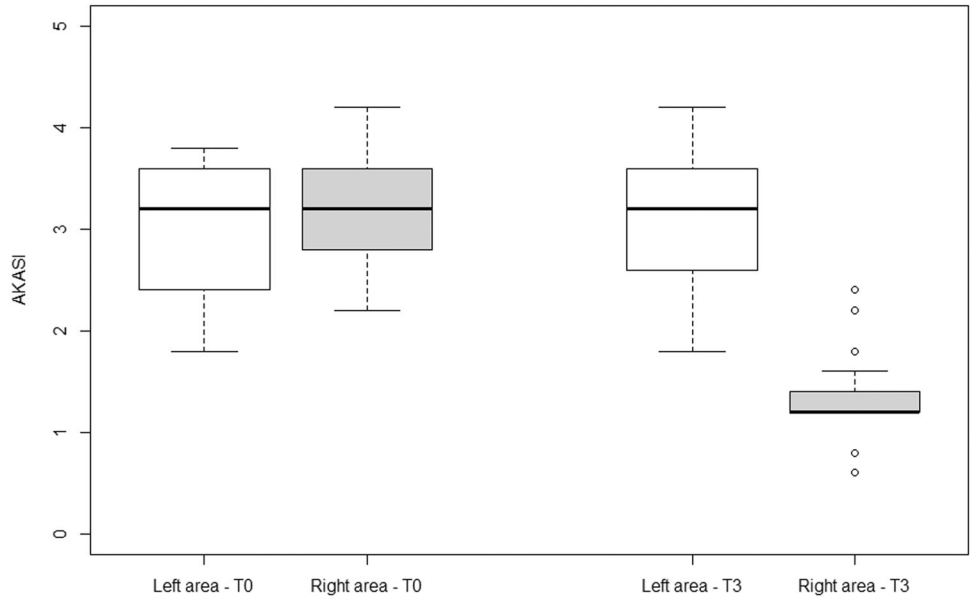

FIGURE 6 Box-plot showing differences in AKASI prior and 6 months after FXL. Wilcoxon test showed significant differences ($p < 0.001$) between AKASI at baseline and at follow-up visit in the right-treated area (gray) while the left-untreated area showed a slight worsening (white). AKASI, actinic keratosis area and severity index.

damaged cells and limiting the expansion on the mutated clones, FXL could potentially reduce the development of AKs in patients at high risk for SCC. As shown in Figure 4, the mean number of AKs decreased from T0 to T1 and further to T3, also suggesting a long-term action of FXL on AKs and the cancerization field. As reported in Table 2, although the mean AKASI values in the untreated area were quite similar at T0 and T3 ($p = 0.20$), the individual values increased between the two time-points, suggesting that FXL could be considered as a preventing tool in patients at high-risk for developing of AKs and NMSCs. In detail, it is possible to consider that while in the treated area the mean value of AKASI decreased after treatment from 3.25 to 1.29, in the LA it

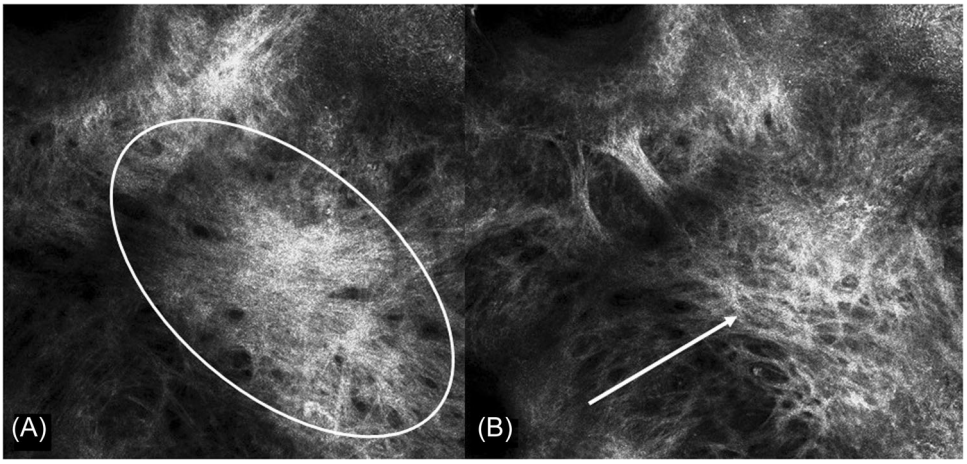

FIGURE 7 RCM. Left area without treatment (A) and right area at 4 months after treatment (B). Irregular and fragmented collagen bundles on the left (A, white circle) and compact and more regular collagen bundles on the right (B, white arrow).

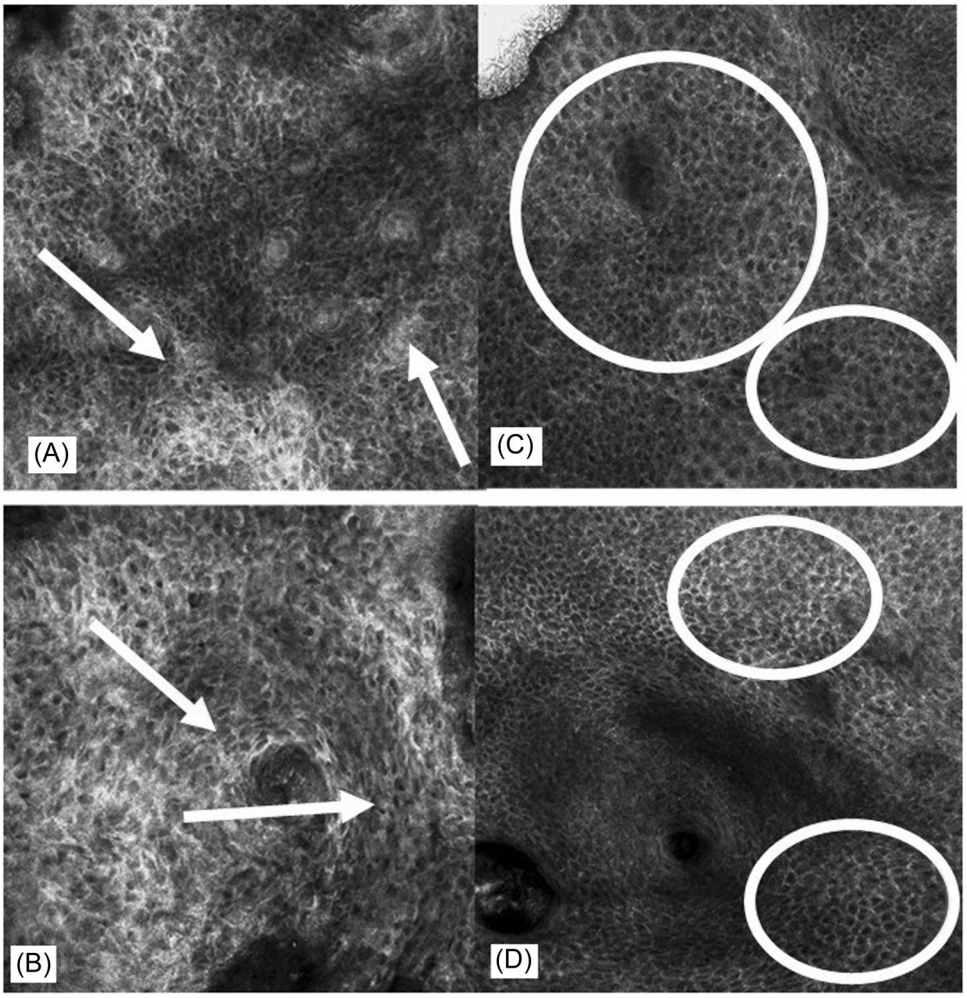

FIGURE 8 RCM. Left area without treatment (A, C) and right area at 4 months after treatment (B, D). Note that on the left side there are atypical keratinocytes (white arrows), whereas a regular honeycomb pattern of the epidermis is highlighted on the right side (white circle).

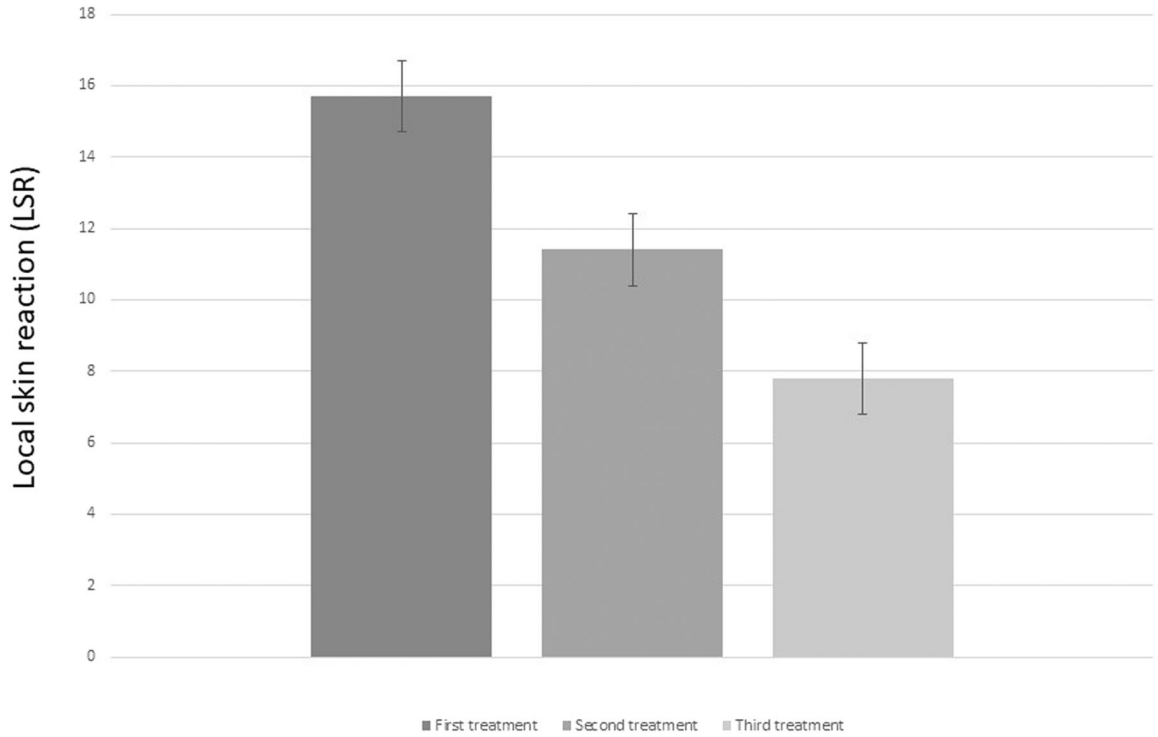

FIGURE 9 Mean local skin reaction (LSR) in all patients. After first treatment 15.7, after second treatment 11.4 and 7.8 after third treatment. Observe the decreasing trend of LSR. The values shown refer to all patients. In no patients it was necessary to postpone or cancel the treatment cycle.

remained the same or almost showed a slight increase from 3.04 to 3.07, explaining that nontreatment of an area could result in a worsening clinical condition. The results that emerged from RCM deserve special mention. This innovative technique allowed us to show a quite complete normalization of subclinical findings associated with AKs and the cancerization field. The evaluation criteria consistently observed by RCM in these cases included keratinocyte atypia, nuclear and cellular pleomorphism, hyperkeratosis, parakeratosis, and solar elastosis. The acquired images and subsequent evaluations showed the absence of clinical relapses at T3 with the lack of subclinical changes in the epidermis and dermis. Thanks to these in vivo evaluations (e.g., reduction of keratinocytic disarray, scales and solar elastosis and normalization of the honeycomb pattern), we were able to confirm the positive effect of FXL on the scalp and to evaluate its maintenance at the follow-up visit after 6 months even on a subclinical level. In addition, the dermal shaping visible under RCM could indicate the role of FXL in both AKs removal and long-term reactivation of senescent fibroblasts with new collagen fibers apposition and correction of the chronic photoaging. However, the persistence of alterations in RCM also in the RA would be referrable to chronic photodamage. In fact, as reported by Pezzini et al.,[42] in patients with photoageing, it is possible to find at epidermal layer presence of irregular honeycomb pattern and mottled pigmentation, at dermo-epidermal junction polycyclic papillary contours and enlarged sebaceous glands and at the upper dermis huddle and curled collagen. Taken together, all the clinical, laboratory, and in vivo results of our study allowed us to confirm that CO_2-FXL can be considered as a valuable tool for the treatment of the cancerization field, both for the management of clinically evident lesions and as a preventive therapy for the occurrence of NMSCs, due to its ability to restore the proper functioning of the paracrine IGF1/IGF1R signaling pathway. However, a longer follow-up period (up to 12 months) should be considered to further emphasize these results and to fully support FXL not only as a cosmetic tool, but as an innovative device for patients with a high risk of developing skin carcinomas.

AUTHOR CONTRIBUTIONS

Emanuele Trovato: Writing and original draft preparation. **Alessandra Cartocci**: Statistical analysis. **Diletta Fiorani**: RCM examination. **Pietro Rubegni**: Review and editing. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

Emanuele Trovato has intermittent project focused consulting and/or advisory relationships or/and travel-congress support with Eli-Lilly, Novartis, Janssen-Cilag, Abbvie, Almirall with no impact on this work. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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