OPEN

ORIGINAL ARTICLE
Technology

Fluorescent Light Energy and Chronic Lesions: A Winning Association

Alberto Crema, MD
Carlotta Scarpa, MD
Regina Sonda, MD
Sandro Rizzato, MD
Giuseppe Masciopinto, MD
Franco Bassetto, MD

Background: Chronic ulcers represent a challenge for healthcare professionals and a large expense for national health care systems for their difficulty in achieving complete healing and for their high incidence of recurrence. With the progressive aging of the general population, the incidence of these injuries will only increase, further affecting the public health budget, hence the need to find new strategies for their management. The purpose of this study was to share the experience of the Complex Operational Unit of Plastic Surgery of the University Hospital of Padua with fluorescent light energy therapy, outlining its role in the treatment of chronic ulcers in the daily use outside the previous EUREKA study.
Methods: In this case series study, we enrolled 15 patients with chronic ulcers of any etiology between January 2018 and July 2019 and we treated them using fluorescence light energy. We evaluated efficacy and safety endpoints reporting data in excel files completed by medical staff during the study.
Results: The study confirms the effectiveness of fluorescent light energy inducing chronic ulcer healing, regardless of etiology, or at least preparing the lesions for a skin graft closure surgery. The system showed a low rate of complications established by patient adherence to treatment. Patients also reported a reduction in pain both at home and during outpatient dressings.
Conclusion: Based on our experience, fluorescent light energy shows an excellent safety and efficacy profile in chronic ulcers no more responsive to traditional dressings and/or surgery. *(Plast Reconstr Surg Glob Open 2021;9:e3667; doi: 10.1097/GOX.0000000000003667; Published online 13 July 2021.)*

INTRODUCTION

Chronic lesions are represented, depending on the etiology, by ischemic, diabetic, venous, posttraumatic, postsurgical wounds and bedsore ulcers that do not re-epithelize within 8–10 weeks.[1] It has been estimated that chronic wounds have an incidence rate of 120 per 100,000 people aged between 45 and 65 years, and it rises to 800 per 100,000 people older than 75 years of age.[2] Chronic ulcers represent a challenge for healthcare professionals, and effective wound management is crucial to assist the healing process.[2,3] In addition, the socioeconomic weight of these injuries represents a huge cost to national health care systems[2,4]: for example, they cost the US health care system more than $25 billion each year.[3]

From the Plastic and Reconstructive Surgery Unit, Department of Neurosciences, University of Padua, Padua, Italy.

Received for publication December 24, 2020; accepted April 21, 2021.

DOI: 10.1097/GOX.0000000000003667

With the progressive aging of the general population, the incidence of these diseases will only increase toward further impact on the health budget.[2,5] Traditional treatments are often inadequate, as they are unable to heal the wound but only to stabilize it, forcing the patient to resort to frequent dressings, hence the need to find new strategies for their management.

Fluorescent Light Energy Therapy

Fluorescent light energy (FLE) is a new type of treatment for chronic ulcers that is gaining a lot of interest in recent years. This therapy is based on low energy light which, as proved by several studies, is able to stimulate a cascade of reactions capable of intensifying the physiological cellular processes involved in the wound healing process.[6,7] Non-ionizing forms of light (laser, LED) in the spectrum of visible or infrared lights induce a nonthermal response that involves endogenous chromophores activating photographchemical and physical cascades at the intracellular level.[8–10] Some of the mechanisms of action of this type of wound healing therapy are the increase in blood flow,[11] the anti-inflammatory action, the cell proliferation, the protein

Disclosure: *Drs. Bassetto and Scarpa are medical consultants for KLOX Technologies. All the other authors have no financial interest to declare in relation to the content of this article. No funding was received for this article.*

synthesis, the antibacterial and anti-mycotic effect, and the reduction of the infections.[2,12]

LumiHeal System

The LumiHeal System, developed by KLOX Technologies Inc, is based on two components: a topical photograph-converter gel (LumiHeal gel) and an LED noncoherent blue activator lamp (KT-H lamp). The gel is made up of two components to be mixed before use and supplied in two separate containers: the transparent carrier gel and the orange chromophore.

The fluorescent technology of the LumiHeal gel is based on the ability of particular molecules (chromophores) to capture light emitted by a blue LED lamp and then to convert it into a different and wider emission spectrum in the visible spectrum (fluorescence) with a longer wavelength and therefore with lower energy[2] (wavelength range emitted: 532–615 nm). Several studies have shown that the most effective wavelengths in penetrating the skin and promoting healing are those of blue, green, yellow, and orange; each wavelength corresponds to a precise biological effect (Table 1)[13–15]; the main feature of the LumiHeal system is precisely that of maximizing the therapeutic effect of photobiomodulation by causing the wound to be irradiated simultaneously by several different wavelengths. The progression of the process is visually controllable, thanks to the color variations of the gel in the various phases: at the time of application, the gel appears orange; the activated gel appears intense yellow and once exhausted it turns pink transparent.

AIM OF THE STUDY

The purpose of this study was to share the experience of the Complex Operational Unit of Plastic Surgery of the University Hospital of Padua with FLE therapy in daily use, outlining its role in the context of traditional treatments used so far.

MATERIALS AND METHODS

Protocol

In this case series, 15 patients with chronic ulcers of any etiology were treated between January 2018 and July 2019 using the LumiHeal system of KLOX Technologies Inc (Table 2). To be enrolled, patients had to comply with the following inclusion criteria:

- The ulcer had to be present and in treatment for at least 3 months without appreciable improvements both with advanced dressings and with a surgical approach;
- Necrosis area had to involve the subcutis up to the muscle fascia without intersecting it;
- There should be no signs of progression of ongoing healing;
- The therapeutic option with FLE had to be proposed by medical personnel experienced in the management of difficult wounds.
- They should not fall within the absolute contraindications described by the manufacturer: pregnancy, breastfeeding, taking photosensitizing drugs, skin hypersensitivity.

Table 1. The Biological Effects Induced by the Different Wavelengths

Blue	Green	Yellow-Orange
Nitric oxide production by endothelial cells and vasodilatation Bactericidal effect	Growth factor production Keratinocyte proliferation and migration Collagen production	Growth factor production ATP synthesis Anti-inflammatory Fibroblast proliferation and migration Collagen production Angiogenesis

Table 2. Information on Treated Patients

ID	Age (y)	Gender	Site	Size	Etiology	Comorbidity
1	43	Man	Sacred Bilateral groin Perineum	5 × 7 cm (perineum) 3 × 2 cm (left groin) 1.5 × 2 cm (right groin)	Postsurgical: hydrosadenitis debridement	Seronegative spondyloarthritis
2	41	Man	Left ischium	3 × 4 cm	Pressure ulcer	Posttraumatic paraplegia
3	54	Woman	Left foot (ankle) Left leg (pretibial)	1 × 1 cm (ankle) 4 × 2.5 cm (pretibial)	Cold burn	Nephrotransplantation, Berger disease, HBP, DVT left leg
4	77	Man	Left leg (ankle)	2 × 3 cm	Posttraumatic	—
5	40	Man	Left leg (pretibial)	15 × 20 cm	Postsurgical: cSCC excision and free flap reconstruction	—
6	45	Man	Right left (pretibial)	10 × 20 cm	Vascular (venous insufficiency)	HCV+, drug addiction, psoriasis, DVT/erysipelas
7	60	Man	Bilateral foot	3 × 4 cm (right) 1.5 × 2 cm (left)	Vascular (arterious insufficiency)	DIC, post S. *Pneumoniae* sepsis
8	60	Woman	Left foot (heel)	1 × 0.5 cm	Posttraumatic	Peripheral vascular disease
9	46	Woman	Right leg	10 × 15 cm	Recluse spider bite	—
10	30	Man	Back	4 × 6 cm	Postsurgical dehiscence	—
11	58	Man	Left foot (heel)	4 × 5 cm	Pressure ulcer	Spina bifida
12	82	Woman	Right leg (ankle)	3 × 4 cm	Vascular (venous insufficiency)	Polycythemia vera, HBP
13	58	Man	Right leg (ankle)	1.5 × 2 cm	Posttraumatic	Obesity, COPD, AF, right DVT
14	23	Woman	Left leg (ankle)	1 × 3 cm	Postsurgical keloid	—
15	59	Woman	Ischium sacrum	10 × 11 cm	Pressure ulcer	HCV+, paraplegia, pluriallergy

Adapted from Barolet, Fushimi et al, Whelan et al.

Typically, before treatment, if excess of fibrin or necrotic tissue was present, surgical outpatient debridement was performed. It was used as per the protocol suggested by the manufacturer: the lesions were cleaned with saline solution and then a 2-mm-thick layer of the LumiHeal gel was applied. The area to be treated subsequently was illuminated with the activator LED (blue light 440–460 nm; power 55–129 mW/cm^2) positioned at 5 cm for 5 minutes. The protocol included biweekly sessions or alternatively one session per week; in this case the application was performed two times (5 minutes + cleaning + 5 minutes). The choice of one or two weekly applications depended on multiple factors: compliance of the patient to go to the hospital twice a week, intrinsic difficulties in transporting elderly patients with comorbidity, severity of the lesions, and availability of surgeries for dressings during the year.

At the end of the session, the exhausted gel was removed with a saline solution, and the lesions were medicated with nonadherent dressings according to the standard of care specific to each type of aetiology. Wounds were treated according to the TIME principle: tissue debridement, infection control, moisture balance, and edges of the wound.[16] Dressing used depended on wound bed: if draining, the dressing of choice was based on polyurethane or hydrofiber sheets; if dry, hydrogels were the dressing of choice.[16,17] All venous ulcers were also treated with a compression wrap.

The patients were treated until complete re-epithelialization or until the wound bed was considered ready to receive a skin graft or for a maximum of 24 weeks. The study was conducted in compliance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice; verbal informed consent was obtained from all patients.

Endpoints

Efficacy Endpoints

As efficacy endpoints it was decided to evaluate:

- The resolution of perilesional inflammation;
- The reduction in size (divided into complete closure; "responder" patients, ie, with a reduction in size more than 50%; "partial responder" patients, ie, patients with a size reduction less than 50% and "nonresponder" patients, ie, patients with an increase in size);
- The adequate preparation of the bottom of the lesion for subsequent grafting in those cases that were not completely closed;
- The absence/presence of infection.

Each of these endpoints was evaluated clinically and reported in excel files at the end of the treatment period by medical personnel experienced in the management of difficult wounds.

Safety Endpoints

As safety endpoints, it was decided to evaluate:

- The onset of adverse events;
- The degree of pain experienced by patients during treatment and at home according to the NRS scale;
- Patient compliance to undergo scheduled sessions.

The degree of pain was assessed by submitting to patients, during each session, the NRS scale relative to the pain experienced during treatment, and the average pain experienced at home between one session and the other. Compliance was assessed considering the presence of patients at the scheduled sessions. In this study, a statistical analysis was not performed due to the small sample size and the descriptive characteristic of the chosen endpoints.

RESULTS

The average age of the patients treated was 52 years (minimum age 23 years; maximum age 82 years), 14 participants were of white race and one was of Bengali ethnicity. The etiology of the lesions was varied, as shown in Table 1: three pressure ulcers, four postsurgical (one outcome of hydrosadenitis submitted to surgical toilette; one outcome of removal of squamous cell carcinoma and subsequent free flap reconstruction; one postsurgical dehiscence, and one outcome of removal of keloid), three post traumatic, three vascular (two from venous insufficiency and one from arterial insufficiency) and two of other aetiology (one cold burn and one violin spider bite outcome). Of the 15 patients who started treatment, one did not complete the expected cycle and abandoned the protocol after about a month and a half (10 total sessions, patient ID 6).

Efficacy Endpoints

Table 3 shows the efficacy results. Complete re-epithelialization was achieved in seven patients (50%), a size reduction more than 50% in five patients (36%), a size reduction less than 50% in one patient (7%), and a worsening in one patient (7%). (Fig. 1) In all cases, including the patient who abandoned the protocol, the perilesional inflammation was resolved at the clinical evaluation. Regarding wound bed preparation, considering the lesions not completely re-epithelized, in five cases the bed was considered suitable for a possible skin graft (71% of patients not completely re-epithelialized), and in two cases not suitable (29%). Finally, in no case were clinical signs of infection detected during the treatment period that required the use of systemic antibiotic therapy. The mean duration of treatment was 13.64±6.63 weeks (Table 3).

Safety Endpoints

Safety results are shown in Table 4. During the treatment period only one patient developed a major adverse event that required treatment to be stopped: the development of a superficial second degree burn with blisters (Patient ID 3) (Fig. 2).

The pain decreased until it disappeared in most cases except one. Table 4 shows the average score obtained from the score during treatment and that at home at time T0 (first session), T1/2 (intermediate session), and T1 (final session) (Table 4).

DISCUSSION

According to our knowledge, at the time of this writing there are only three clinical studies in the literature on the

Table 3. Efficacy Endpoints

ID	Perilesional Inflammation	Response	Bed Preparation	Duration of Treatment	Infection
1	Absent	Responder	Suitable for grafting	12 weeks	Absent
2	Absent	Complete closure	—	15 weeks	Absent
3	Absent	Responder	Suitable for grafting	14 weeks	Absent
4	Absent	Complete closure	—	3 weeks	Absent
5	Absent	Complete closure	—	15 weeks	Absent
6	Absent	—	—	—	—
7	Absent	Responder	Suitable for grafting	8 weeks	Absent
8	Absent	Complete closure	—	6 weeks	Absent
9	Absent	Complete closure	—	8 weeks	Absent
10	Absent	Nonresponder	Not suitable for grafting	8 weeks	Absent
11	Absent	Responder	Suitable for grafting	21 weeks	Absent
12	Absent	Responder	Suitable for grafting	24 weeks	Absent
13	Absent	Partial responder	Not suitable for grafting	24 weeks	Absent
14	Absent	Complete closure	—	14 weeks	Absent
15	Absent	Complete closure	—	19 weeks	Absent

LumiHeal system.[2,6,18] These previous studies have focused on the most frequent etiology of chronic lower limb ulcers: venous ulcer, pressure ulcer, and diabetic foot ulcer. Our study instead focused on chronic ulcers regardless of etiology precisely because it is set in a context of a routinely ambulatory setting. The protocol included one or biweekly sessions depending on various factors as seen above. In our study in only five cases (33%), we used the twice weekly application, in patient IDs 1, 2, 6, 11, and 12. The low use of the double weekly application was mainly due to the patient's low availability to come more times a week at the hospital; this data can be traced back to the routinely ambulatory setting of the study: these patients in fact had a long history of unsuccessful surgical treatments and dressings resulting in a low confidence in the hospital and healthcare personnel. During the Christmas and summer holidays instead, for organizational reasons (reduction in the number of clinics and of the nursing staff), the single weekly application was proposed directly.

The study showed an excellent efficacy profile: of the 14 patients who completed the study we obtained seven patients (50%) classified as "complete closure," five patients (36%) as "responder," one patient (7%) as "partial responder," and one patient (7%) as "nonresponder."

The mean time for complete closure was 11.43 ± 5.80 weeks; its important to underline that any degree of improvement in the local condition (93% of the patients considering the "partial responders," the "responders," and the patients who have achieved complete re-epithelialization) was obtained in patients who were being treated at our hospital for at least 3 months without appreciable improvements both with advanced dressings and with a surgical approach and that showed no signs of progression of healing. One of the most interesting features of photobiomodulation therefore appears to be the ability to reactivate the healing process in chronic lesions. These results are in line with other clinical studies that tested the effectiveness of the FLE therapy using the LumiHeal system: in the EUREKA (Evaluation of Real-life Use of Klox Biophotonic System in Chronic Wound Management) study a complete healing rate of 52% was obtained in the "interim" work[2] and 47.5% in the final publication[6]; Nikolis et al[18] in his efficacy study on venous ulcers, on the other hand, achieved a complete healing of 44.4%. Although our study is not directly comparable with the previous ones, and in turn these among them, due to the different etiology of chronic ulcers, the different sample size, the different type of patients, and the different inclusion and exclusion criteria, this substantial overlap of the results reinforces the efficacy profile highlighted and our positive opinion on this type of treatment.

Unlike the previous studies already mentioned, in our study among the efficacy endpoints it was decided to also evaluate perilesional inflammation because, as is known, chronic wounds generally tend to remain blocked in the inflammatory phase of the healing process. In all cases, the clinical signs of perilesional inflammation (rubor, dolor, calor, tumor, functio laesa) were resolved confirming the anti-inflammatory power of FLE therapy already highlighted in other preclinical studies.[19–21] In particular, it is known how FLE/photobiomodulation is able to induce the modulation of the nuclear factor Nf-kB, which controls both proinflammatory and anti-inflammatory factors such as interleukin-1 (IL-1), IL-8, cyclooxygenase-1 (COX-1), and COX-2.[19–21] Ferroni et al[22] demonstrated how FLE has a beneficial effect on mitochondrial homeostasis in inflamed cells, favoring mitochondrial ATP production by upregulation of uncoupling protein 1 (IUCP1) and carnitine palmitoyltransferase 1B (CPT1B) genes.

Considering the patients who did not reach complete re-epithelialization (7.50%), five were judged to be suitable for grafting at some point of the treatment (71%); the two cases not considered suitable for grafting belonged to the "partial responder" and "nonresponder" categories.

During the treatment period, no patient required systemic antibiotic therapy and no patient developed clinical signs of contamination that required the use of topical antimicrobial agents (Fig. 3).[23]

In the analysis of the efficacy profile, the case of patient ID 5 is particularly interesting: as can be seen from Figure 3, the bloody area remaining 3 months after free flap reconstruction has completely re-epithelialized with areas with its own pigmentation. This result can be explained by a regenerative effect of FLE determining a stimulation of the proliferation and migration of melanocytes at the lesion level.[10] This aspect of FLE/photobiomodulation, according to our knowledge, has been little investigated and the only study present in the literature[24]

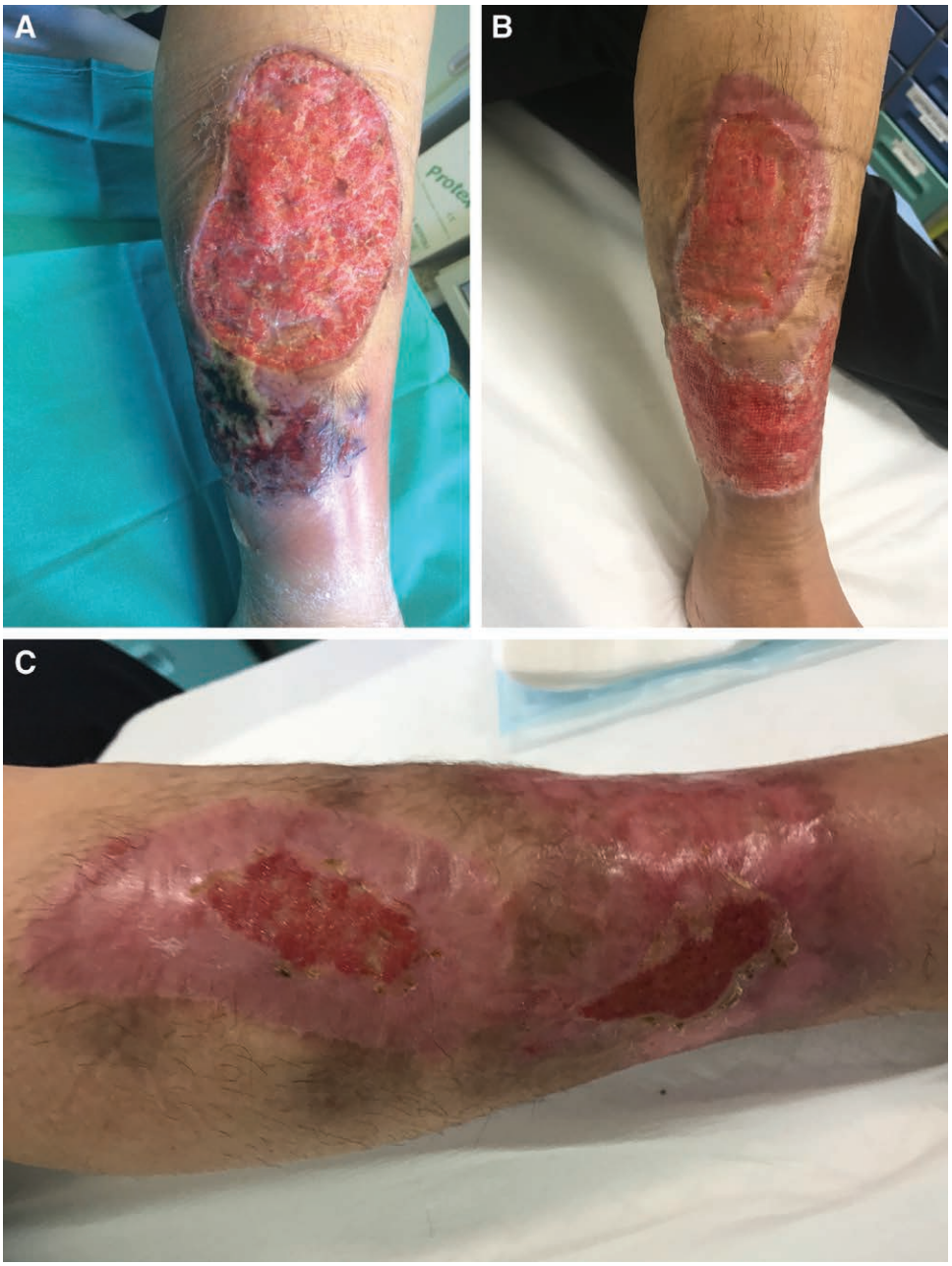

Fig. 1. Progression of the lesion during treatment of patient ID 9. A, At time 0. B, After 1 months. C, After 2 months.

has shown how this therapy is able to induce the differentiation of melanocyte stem cells; migration of immature melanoblasts; melanogenesis and migration of differentiated melanoblasts; and proliferation and migration of perilesional melanocytes. The mechanism by which all this occurs has not yet been well defined but the cytochrome-c oxidase seems to be involved, within the mitochondria, as a photograph-acceptor capable of stimulating regenerative intracellular pathways.[4] This interesting potential of FLE deserves to be deepened with further preclinical and clinical studies and opens new therapeutic perspectives within regenerative medicine.

As in previous studies, the LumiHeal system showed an excellent safety profile: there was only one adverse event, which forced the suspension from the study. The adverse event under examination consisted in the development of a superficial second degree burn with blisters (patient ID 3, Fig. 2), at the perilesional skin level; the lesion healed with an outpatient medication cycle in 10 days without complication. The adverse event was reported to the manufacturer and to the competent authorities. The patient under examination in anamnesis had many comorbidities (see Table 2); it is not possible to identify a clear predisposing factor for the development of this side effect even though the comorbidities

Table 4. Safety Endpoints

ID	Adverse Events	Pain (NRS Scale) T_0	$T_{1/2}$	T_1	Compliance
1	No	8	4	0	Present at all sessions
2	No	6	0	0	Present at all sessions
3	Development of superficial second degree burn in pretibial region	7	2	6	Present at all sessions before suspension
4	No	6	0	0	Present at all sessions
5	No	7	0	0	Present at all sessions
6	No	8	—	—	Present at all sessions before suspension
7	No	6	0	0	Present at all sessions
8	No	5	0	0	Present at all sessions
9	No	9	4	0	Present at all sessions
10	No	4	2	2	Present at all sessions
11	No	4	2	0	Present at all sessions
12	No	6	0	0	Present at all sessions
13	No	7	4	2	Present at all sessions
14	No	0	0	0	Present at all sessions
15	No	0	0	0	Present at all sessions

Wound bed preparation suitable for grafting: granulating ulcer bottom, in the absence of fibrin or debris.

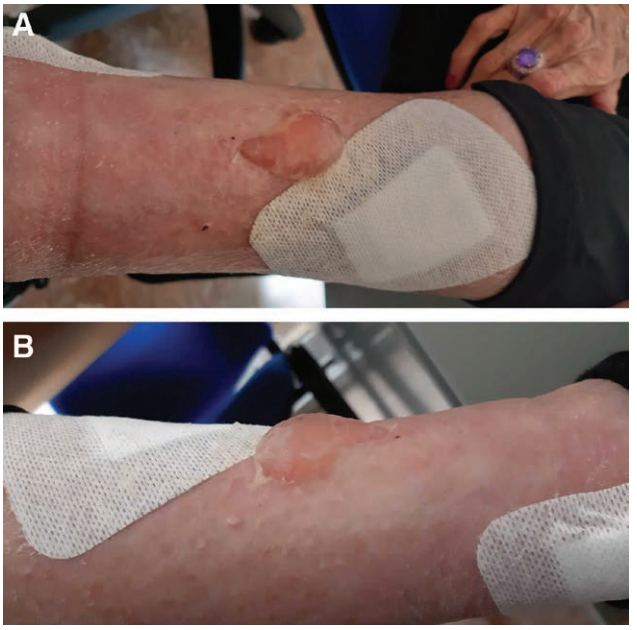

Fig. 2. Adverse event development in patient ID 3. Superficial second burn on perilesional skin in pretibial region. A, Front view. B, Lateral view.

may have influenced, especially the nephrotransplantation with the associated therapy. Despite the adverse event and the abandonment of treatment, patient ID 3 was considered a "responder" since at the time of abandonment there had been a reduction in size (>50%) with complete coverage of the Achilles tendon that at the time of taking charge was completely exposed. Although it was judged suitable for grafting, it was preferred to continue with outpatient medications for the little extension of the residual lesion obtaining complete re-epithelialization in about 3 months.

In all but one patient, there was a significant reduction in pain from the first sessions. Of the 12 patients who

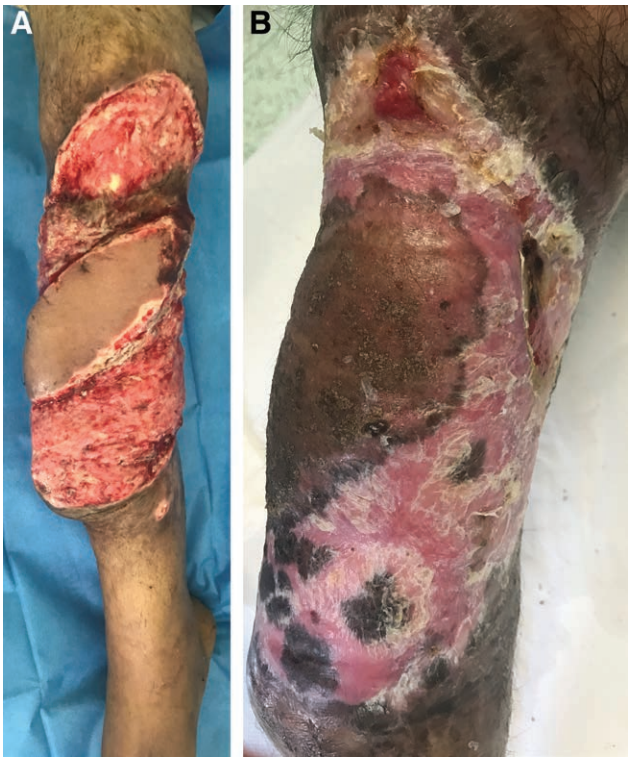

Fig. 3. Progression of the Lesion during Treatment of patient ID 5. A, At time 0. B, After 3 months.

reported experiencing pain at T0 (patient ID 6 who abandoned treatment was excluded), nine (75%) at the end of treatment said they no longer experienced pain, two (17%) that it was much decreased, and one (8%) substantially stable; the latter value refers to patient ID 3, who developed the adverse event described above and the T1 value reported is that declared in the last session which led to the development of the burn. Even in this patient there had initially been a significant reduction in pain; this is an important aspect of FLE therapy already highlighted in previous studies[2,6,18] which partly justifies the high compliance found in this study (100%).

Of the 15 patients who started treatment, one did not complete the expected cycle and abandoned the protocol after about a month and a half (10 sessions in total, patient ID 6). Of this patient, given the relatively early abandonment, it was decided to consider among the endpoints only the perilesional inflammation and the occurrence of adverse events until the withdrawal from the study. Regarding compliance, it was considered 100% because until the withdrawal from the study the patient presented himself to all the scheduled sessions and because the abandonment did not depend on adverse events or other causes attributable to the FLE therapy. The real reasons for abandonment in this case depended on serious personal problems and the patient's history of drug addiction; after leaving the study, the patient no longer performed any medication and/or visit in our clinics.

This study, despite highlighting excellent safety and efficacy profiles of the FLE therapy in the solution proposed by KLOX Technologies Inc, has several limitations: the absence of a control group; the low sample size and

the limited number of inclusion and exclusion criteria (which led to the study having very different lesions in terms of etiology and size); the subjective evaluation of some endpoints; and the potential bias in the evaluation by different authors.

CONCLUSIONS

Based on this study, although developed with a low sample size and without statistical value, and our clinical experience with the LumiHeal system of KLOX Technologies Inc, we believe that FLE therapy may have an important role in the treatment of chronic ulcers nonresponsive to other traditional treatments. FLE therapy has confirmed to have an excellent efficacy and safety profile and to be well tolerated by patients. Thanks to these results, supported by the literature, it has been implemented in the solution proposed by KLOX Technologies Inc within the Complex Operational Unit of Plastic Surgery of the University Hospital of Padua as treatment of chronic ulcers that are not responsive to medications and/or surgical treatments. We believe that further studies are needed to investigate the potential of FLE therapy and that for a more complete efficacy profile, it would be necessary to extend the study with a control group and with follow-up checks at 3, 6, and 12 months to verify the injury recurrence rate.

Alberto Crema, Resident MD
Plastic and Reconstructive Surgery
Unit, 2 Nicolò Giustiniani Road
Padua 35128, Italy
E-mail: dr.acrema@gmail.com

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