

## ORIGINAL ARTICLE

# A biological therapeutic challenge for chronic ulcers: results of a clinical pilot study

## Una sfida terapeutica di tipo biologico per le ulcere croniche: risultati di uno studio clinico pilota

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### Abstract - Riassunto

**BACKGROUND:** Chronic ulcers, including diabetic ulcers, pressure ulcers, venous ulcers, and arterial insufficiency ulcers, are both difficult and expensive to treat and are an increasingly important challenge for the dermatologist, especially in relation to the growing problem of antibiotic resistance as very often the skin ulcers are optimal sites for bacterial proliferation and the poorly controlled use of antibiotics, even topically and not only systemically, has led to the development of multidrug-resistance that limits its effectiveness. Photodynamic therapy (PDT) seems to have antimicrobial activity in skin infections. It also appears to be effective in stimulating fibroblasts and consequently in the reparative processes involved in wound healing. The objective of this pilot study is to evaluate clinically the therapeutic efficacy, both antimicrobial activity and promoting wound healing, of PDT in skin ulcers of various etiology, which have shown difficulty in healing, with failure for over 1 year of conventional therapies used. **METHODS:** Ten patients, 3 males and 7 females, mean age of 72.5 years, range 56-86 years, who had chronic ulcers with overlapping bacterial infections, sometimes multiple, from the beginning, were enrolled. The skin ulcers were treated with 5-aminolevulinic acid gel, in occlusion for 45-60 minutes; then the surfaces was exposed to 630 nm red light for 10 minutes. The single patient was treated once a week, for 4-16 weeks, depending on the therapeutic response and healing rapidity.

**RESULTS:** All patients achieved ulcer resolution, with excellent treatment tolerability and easy daily home medication between sessions, without the need for antibiotic therapy, despite the presence of bacteria in the lesion.

**CONCLUSIONS:** These results indicated the PDT is valid therapeutic option for the resolution of difficult ulcers of different etiologies, it avoids the use of antibiotics and it is well tolerated and effective even for those cases of ulcers infected with multi-resistant germs.

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**KEY WORDS:** Photochemotherapy; Skin ulcer; Drug resistance, multiple.

**OBIETTIVO:** L'obiettivo di questo studio pilota è quello di valutare l'efficacia terapeutica, sia in termini di attività antimicrobica che di attività promotrice la riparazione cutanea delle ferite, della terapia fotodinamica nelle ulcere cutanee di varia eziologia, che hanno mostrato difficoltà alla guarigione, con insuccesso da oltre 1 anno delle terapie convenzionali utilizzate.

**METODI:** Sono stati arruolati dieci pazienti, 3 maschi e 7 femmine, con età media di 72,5 anni, range 56-86 anni, che presentavano ulcere croniche con infezioni batteriche sovrapposte, talora multiple, al momento dell'arruolamento. La superficie delle ulcere è stata trattata con acido 5-aminolevulinico in gel, in occlusione per 45-60 minuti, e quindi esposta alla luce rossa di 630 nm per 10 minuti. Il trattamento è stato ripetuto settimanalmente per un periodo variabile da 4 a 16 settimane, a seconda della risposta terapeutica e della velocità di guarigione.

**RISULTATI:** Tutti i pazienti hanno raggiunto la risoluzione delle ulcere, con ottima tollerabilità del trattamento e facilità alla medicazione domiciliare quotidiana negli intervalli fra le sedute.

**CONCLUSIONI:** In conclusione la terapia fotodinamica rappresenta una valida alternativa terapeutica per la risoluzione delle ulcere difficili di varia eziologia e permette di evitare l'utilizzo di antibiotici, risultando efficace anche per quei casi di ulcere infette da germi multiresistenti.

Leg ulcers are often infected, painful, debilitating and reduce a patient's quality of life. Increasing antibiotic resistance is one of the most important and urgent challenges

facing medicine worldwide and requires commitment and study to find alternative, innovative and efficient therapeutic strategies.<sup>1</sup>

Photodynamic therapy is perhaps a possible answer,<sup>2-4</sup> or in any case an opportunity for both of the above problems: in fact it has shown efficacy against bacterial, fungal and even viral infections,<sup>5,6</sup> where the possibility of reaching the pathological tissue was not reduced by crusting barriers and/or hyperkeratotic thickening.

After an accurate cleansing and a careful removal of the fibrinous and necrotic material, the ulcer represents an optimal field of activity for the PDT. This treatment develops in two phases: the first phase is represented by the contact of the ulcer with the photosensitizer, aminolevulinic acid in occlusion, for the time necessary for the cellular absorption of the product; the second phase, of exposure, when the ulcer is exposed to red light at 630 nm, irradiance 90 J at 10 cm (AlphaStrumenti, Milan, Italy) for 10 minutes.

The result of the single session results in a progressive abatement of the microbial charge and following, surprising, resumption of wound repair, with reduction of pain symptoms (pain intensity was assessed by means of VAS) and a marked reduction in healing times.<sup>7-9</sup> The home management of the ulcer is extremely important, with daily medications, which must be simple to perform, possibly with a single product, non-sensitizing, non-irritating, non-aggressive, so to speak, physiological.<sup>10</sup>

## Materials and methods

Patients who have turned to the dermatological outpatient clinic for skin ulcers, of various etiology, present for at least 1 year with little tendency to recovery, despite continuous therapies, have been enrolled for this pilot study. All enrolled patients underwent weekly PDT sessions, until complete healing of the ulcers. The healing time was variable, as was the number of PDT sessions (4 to 16), depending on the initial wound diameter (3-10

cm), the etiology (diabetic, pressure, vascular, traumatic, postsurgical, autoimmune) and the patient's general state of health. The total period of this study (therapeutic phase + follow-up period) was 16 months.

Between one session and the next the ulcers were disinfected with benzalkonium chloride, medicated once a day with a mixture of polyethylene glycol in gel (PEG) combined with allantoin, a synthetic but physiological substance, and bandaged with a light bandage.

At time 0 and after 8 sessions a swab for microbiological culture was performed. At each session the ulcers, after cleansing with physiological solution at room temperature, were premedicated in occlusion with 5-ALA gel (5-ALA with polyoxamers produced by Alpha Strumenti srl, Milan, Italy).

After about 45-50 minutes the degree of cellular absorption of the photosensitizer was checked by checking with visible violet light at 405 nm (typical red fluorescence of positive cells).

Once the complete absorption was established (otherwise the incubation time was extended), the ulcers were exposed directly to the red light at 630 nm irradiance 90 Joule at a distance of about 10 cm for 10 minutes.

At the end of exposure to red light the ulcers were medicated with PEG + allantoin and bandaged.

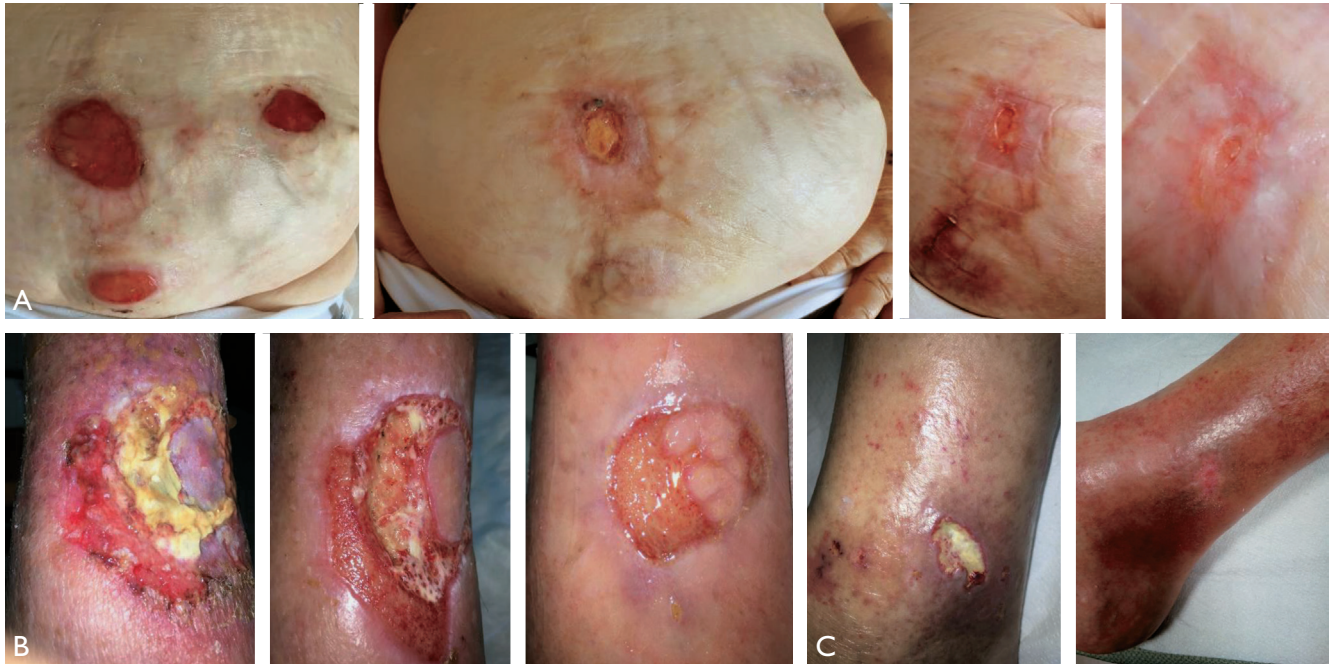
At home the dressing, performed daily, consisted of a simple disinfection with benzalkonium chloride and application of the gelled mixture of PEG and allantoin, with subsequent light bandage.

## Results

Ten patients (Table I) were treated, including 7 females and 3 males, with an average age of 72.5 years for a range of 56-86 years. All patients had unilateral leg ulcers for over 1 year, painful and with poor tendency to heal.

TABLE I.—Characteristics of the 10 patients enrolled in the study.

Patients	Sex	Age	Ulcer type	Ulcer localization	N° of sessions
1	F	56		Ankle	10
2	F	61	Vascular	Leg	8
3	F	62	Diabetic	Leg	8
4	M	65	Diabetic	Leg	4
5	F	71	Vascular	Leg	7
6	M	77	Postsurgical	Abdomen	16
7	F	80	Autoimmune (LED)	Ankle	8
8	M	83	Vascular	Leg	10
9	F	84	Vascular	Leg	8
10	F	86	Postsurgical (skin graft necrosis) and autoimmune (pemphigoid)	Leg	12



**Figure 1.**—A) Patient #6: results at session 16; B) patient #10: results at session 12; C) patient #: results at session 4.

A swab for culture examination was performed at time 0, a positive result in all 10 cases, with the presence of different bacteria in the various patients: *S. aureus*, *S. epidermidis*, *S. mutans*, *Enterococcus faecalis*, *E. coli*, *P. aeruginosa*. In some cases the positivity of the swab could be considered due to opportunistic bacteria, which we believe however could slow down the normal wound repair process.

Only two cases showed the coexistence of more than one germ at the same time: *S. aureus* + *P. aeruginosa* and *Enterococcus faecalis* + *E. coli*. No fungi were detected. In no case has antibiotics been prescribed, either local or systemic.

The application of 5-ALA in occlusion for a time ranging from 45 to 60 minutes did not give hypersensitivity or irritation reactions. No patient complained of pain or itching.

The number of photodynamic therapy sessions (PDT) was variable in the 10 cases treated, from 4 to 16 sessions, depending on the size of the ulcer and the etiology, sometimes due to systemic disease, and/or the patient's general condition.

All patients achieved complete resolution of ulcers with restitutio ad integrum and rapid disappearance of pain symptoms. In all cases the only outcome that could have been recorded consisted in a skin dyschromia that traced the mold of the ulcer, as a stigma of what had been. At the follow-up visit at 1 year after the end of the treatment, no patient showed a recurrence of the treated ulcers (Figure 1).

## Discussion

The use of PDT to treat difficult ulcers, even complicated by overlapping infections, seems to give valid results and promising uses.<sup>4-6</sup> Use on ulcers is optimal since the possibility of exposing the area to be treated directly to red light is easy to perform.

If the extent of the ulcers were higher than the radiation screen, exposure of the area to be treated can be performed at subsequent intervals, moving the lamp and shielding the areas already treated. The use of 5-ALA has given excellent tolerability and safety results, even on damaged skin.

All ulcers taken care of, present for over 1 year and with a poor tendency to cure, have had an important benefit reaching the complete resolution of the wound, with restitutio ad integrum. Our opinion is that PDT has a double effect on ulcers: an advantage in bacteriostatic terms on the micro-organisms present, probably acting on the biofilm, and a direct stimulus on the reparative process with a positive effect on both keratinocytes and fibroblasts.<sup>9-11</sup>

## Conclusions

We believe that photodynamic therapy is an excellent opportunity for the therapy of chronic ulcers. It is applicable in all types of ulcers, regardless of the etiology, even on infected wounds and allows not to use drugs, thus overcoming the problem of antibiotic resistance, present in

many cases of chronic ulcers. It makes use of products and mechanisms that we could define as “biological” as they approach the skin physiology (5-ALA, PEG, Allantoin) and environmental (red light).

The precise mechanism of action of this therapy remains to be investigated and clarified, structuring a targeted experimental study, with a greater number of patients enrolled for treatment and a control group.

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**Conflicts of interest.**—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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