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ORIGINAL PAPERS

Assessment of therapeutic response to photodynamic therapy with the Zn-Phthalocyanine RLP068/Cl *versus* topical Clindamycin in patients affected by Hidradenitis Suppurativa: a comparative clinical pilot study

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Abstract

Hidradenitis suppurativa is a chronic skin disorder characterized by painful inflammatory nodules and abscesses, significantly impacting patients' quality of life. Current treatment strategies, including topical antibiotics, often yield limited efficacy and pose risks of antibiotic resistance. Photodynamic therapy has emerged as a potential option, with RLP068/Cl (ELKO-FAST®, non-sterile formulation) showing promising efficacy due to its broad-spectrum bactericidal activity. We conducted a pilot study assessing the therapeutic response to photodynamic therapy with RLP068/Cl versus topical clindamycin gel in patients affected by hidradenitis suppurativa of Hurley score I, II, and III. Results revealed higher efficacy of photodynamic therapy in combination with RLP068/Cl, particularly in mild cases. Its efficacy remains reliable even in more severe cases when combined with adalimumab. The observed faster lesion improvement and pain relief were ascribed to the bactericidal effects of RLP068/Cl against $Gram^+$ and $Gram^-$ bacteria. Furthermore, photoactivated RLP068/Cl was well tolerated with no adverse events reported. Therefore, photodynamic therapy following RLP068/Cl application represents a novel therapeutic option for hidradenitis suppurativa with potential implications for antibiotic stewardship in dermatology.

E. Rosi and F. Prignano contributed equally to this work.

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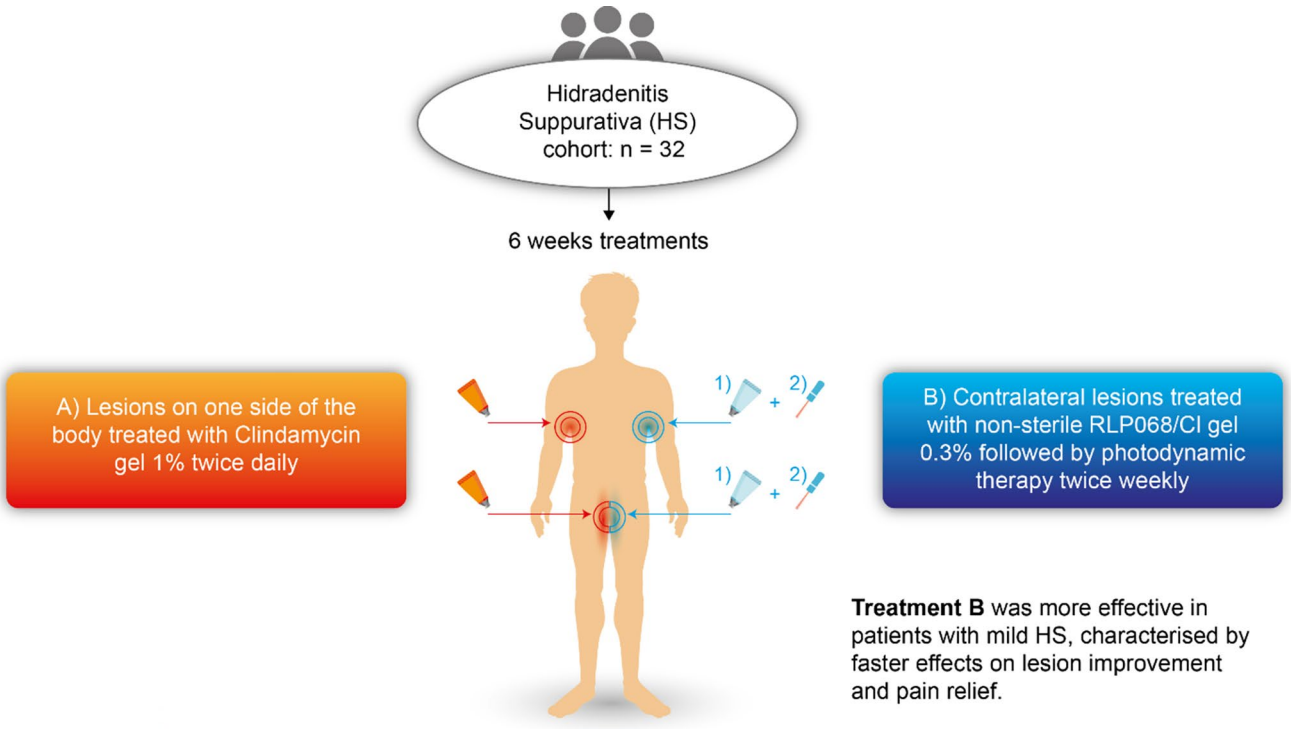
Graphical abstract



Keywords Hidradenitis suppurativa · Photodynamic therapy · Non-sterile RLP068/Cl · Pain relief · Bactericidal activity · Antibiotic stewardship

1 Introduction

Hidradenitis suppurativa (HS) is an uncommon chronic skin disorder, with a global prevalence of 1–4%, characterized by deep-seated, painful inflammatory nodules and abscesses with draining tunnels mainly located in the major body folds [1]. It usually arises during adolescence and early adulthood, causing significant discomfort and embarrassment, which often result in decreased quality of life (QoL), hindered daily activities and enhanced rates of concurrent depression and anxiety [2, 3]. The pathogenesis of HS entails a complex interplay of several factors, including follicular hyperkeratosis of the pilosebaceous–apocrine gland unit, resulting in follicular plugging and eventual rupture with the consequent release of follicular contents into the surrounding dermis. Additionally, the dysregulation of the cutaneous microbiome and bacterial super-infection activate the innate immune system, thereby inducing secondary inflammation of the apocrine glands [2, 3]. Various bacteria, such as *Staphylococcus aureus*, coagulase-negative staphylococci, *Corynebacterium* species, and anaerobes such as *Porphyromonas*, *Prevotella*, and *Fusobacterium* have been identified in deep HS lesions [4]. These microorganisms may contribute to HS pathogenesis by serving as molecular triggers of inflammation. Autoinflammation is linked with dysregulated inflammasome activation and the consequent production of inflammatory cytokines [2, 3]. Various therapeutic approaches, targeting one or more pathogenetic factors, are available [5]. The treatment strategy is guided by the Hurley staging system, a widely used grading method to characterize the extent of disease in patients with HS, categorizing them into three groups (mild, moderate, severe) based largely on the presence and level of lesions, scarring, and sinus tracts [2, 6, 7]. Topical treatments are used as monotherapy for mild cases and in conjugation with systemic therapies, including oral antibiotics, oral retinoids, and antitumor necrosis factor α (TNFα) and anti-interleukin 17 (IL-17) antibodies for more severe cases [6]. Topical antibiotics (e.g. clindamycin 1–2% solution/gel and erythromycin 3% gel) are typically well tolerated, although their effectiveness can be limited and unpredictable among patients, with the risk of developing antibiotic resistance and selecting aggressive bacterial strains. Therefore, new topical treatment approaches have been explored, including photodynamic therapy (PDT) with topical or intralesional application of aminolevulinic acid (ALA), methyl aminolevulinate (MAL)

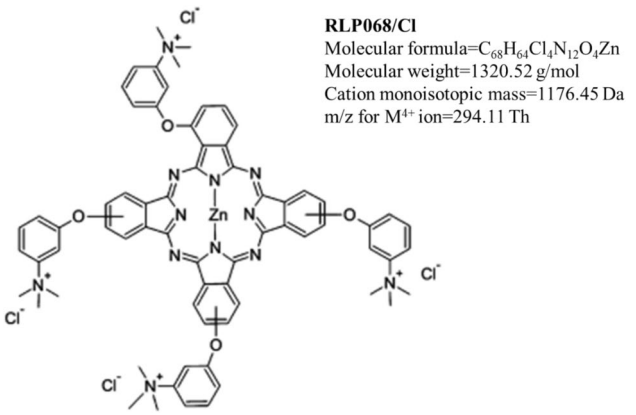


Fig. 1 Molecular characterization of tetracationic Zn(II)-phthalocyanine derivative RLP068/Cl: formula, mass, and ionization properties

[8], and methylene blue [9, 10]. However, these approaches have given contrasting results, particularly regarding their efficacy against biofilms and antibiotic-resistant strains, with both positive and negative outcomes for Gram + and Gram- bacteria (see details in the discussion). In this context, RLP068/Cl (ELKOFAST®, non-sterile formulation) is a novel amphiphilic tetra-cationic derivative of Zn(II)-phthalocyanine (Fig. 1), that, upon photoactivation with red light (wavelength range 600–700 nm), generates singlet oxygen and other reactive oxygen species, affecting a variety of cellular components (e.g. cell membranes and/or cell walls, cytoplasm, and cellular structures). In various in vitro and in vivo studies, RLP068/Cl demonstrated an effective photosensitizing activity against $Gram^+$ and $Gram^-$ bacteria, yeasts, and dermatophytes [11–13], along with limited sensitization of keratinocytes and the inability to penetrate transcutaneously [14, 15]. Hereby, we present the results of a comparative intra-patient pilot study investigating the effect of PDT in combination with RLP068/Cl versus clindamycin gel in the treatment of HS patients.

2 Materials and methods

2.1 Design and population

This side-to-side comparative study was designed to minimize the bias of the different anatomy sites usually affected in HS. Adult patients with symmetrical groin or axilla HS lesions ($n = 32$) were recruited from the HS outpatient clinics of the University of Brescia and the University of Florence, Italy. Clinical and anamnestic data were collected at baseline (T0) (Table 1). All patients signed a written informed consent. Exclusion criteria included individuals who had used retinoids, tetracyclines, or other photosensitizing medications within the past six months, as well as pregnant or breastfeeding women. At baseline, HS severity was assessed using the Hurley staging system, which categorizes the patients into: stage I, used for solitary or multiple isolated non-scarring abscess formations; stage II, for recurrent, single, or multiple, widely abscesses surrounded by normal-looking skin, with limited cicatrisation and/or straight sinus tracts; stage III, for diffuse or broad involvement, characterized by multiple coalescent abscesses, interconnected sinus tracts, and extensive scarring. The severity of the disease was also assessed using both the HS physician's global assessment (HS-PGA) and the international HS severity score system (IHS4), which incorporate various clinical evaluation criteria, and categorize disease severity into mild, moderate, and severe based on the patient's total score [16]. Naïve patients with Hurley score I and II who received topical treatment only, chronic patients with Hurley stage II, and those with Hurley stage III showing stable partial improvement with adalimumab therapy for at least 6 months were enrolled. The treatment lasted 6 weeks, and the assignment to one of the treatments was randomly determined. Ultrasound (US) evaluation was conducted at baseline and follow-up examinations using sonographic staging of HS severity (SOS-HS) (Fig. 2). US assessments were performed before and after the treatment using linear and compact multifrequency probes with an upper range of 14–20 MHz. Color Doppler US and power Doppler US (MyLab™ One, Esaote S.p.A., Genoa, Italy) were utilized to detect vascularity in the lesional areas. The US technique for examining HS skin lesions was previously described by

Table 1 Clinical and anamnestic data of the study population at T0

	Patients ($n = 32$)
Gender, *n (%)*	
Male	15 (46.9%)
Female	17 (53.1%)
Age, mean ± SD	33.4 ± 11.1
BMI, mean ± SD	25.6 ± 3.9
Smokers	28 (88.0%)
Hurley score, *n (%)*	
[1]	10 (31.2%)
[2]	16 (50.0%)
[3]	6 (18.8%)
HS-PGA, mean ± SD	2.8 ± 0.6
IHS4, mean ± SD	7.6 ± 5.0
SOS-HS, *n (%)*	
[1]	8 (25.0%)
[2]	16 (50.0%)
[3]	8 (25.0%)

Abbreviations: *BMI* body mass index, *HS-PGA* hidradenitis suppurativa physician's global assessment, *IHS4* international hidradenitis suppurativa severity score system, *SOS-HS* sonographic scoring system of hidradenitis suppurativa

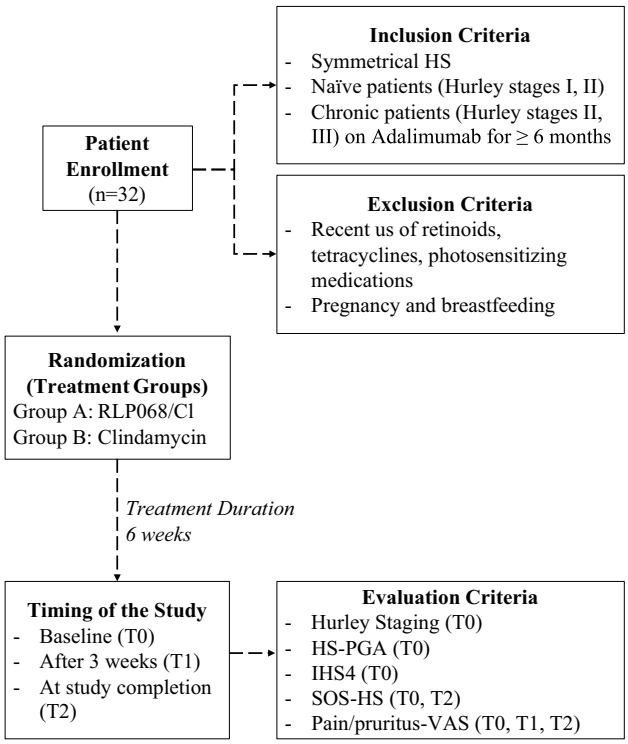


Fig. 2 Visual scheme of the study design, outlining the patient enrollment, randomization, treatment groups, follow-up time points, and evaluation criteria

Wortsman and colleagues [17]. Pain and itch were assessed using a visual analogue scale (pain-VAS) and pruritus using a visual analogue scale (pruritus-VAS).

2.2 Treatments

Lesions on one side of the body were treated by the patients at home with clindamycin gel (Clindamycin SAME gel 1%, Savoma Medicinali S.p.A., Parma, Italy) twice daily for 6 weeks. The contralateral lesions underwent a total of 12 PDT treatments (twice weekly for 6 weeks) in a hospital setting. However, it could potentially be administered at home as well, using available LED light sources with a 630 nm peak. The PDT procedure was performed as follows: a gel formulation containing RLP068/Cl (ELKOFAST® gel 0.3%, non-sterile formulation, Molteni Farmaceutici, Scandicci, Italy) was applied under an occlusive and opaque dressing (a non-transparent gauze under Tegaderm™ adhesive patch) after thorough cleansing with a physiological solution. RLP068/Cl gel was applied at a rate of 1 ml per 25 cm^2. According to the manufacturer's recommendations after 30 min, the dressing was removed, and the skin was irradiated for 8 min with 60 J/cm^2 of 630 nm red light from an LED lamp (VULNOLIGHT®, Molteni Farmaceutici) with a fluence of 125 J/cm^2. The exposure duration of 8 min was determined based on the manufacturer's recommended guidelines, ensuring optimal conditions for the treatment's efficacy and safety; moreover, this exposure duration had proven to be effective and safe in a previous preliminary study on diabetic foot [18].

Patients were prospectively assessed after 3 (T1) and 6 (T2) weeks. Clinical end points were defined as follows: "complete response" if inflammation and abscesses were absent and the patient did not report pain; "partial response" indicating improvement of clinical lesions with only reddish areas in the absence of abscesses and/or symptoms; and "no response" if lesions did not improve. Interconnected fistulas, non-inflammatory cysts, and scarring were not considered due to their anatomical chronicity despite changes in inflammatory status. Patients' pain level was also assessed using the VAS at each time point.

2.3 Statistics

Descriptive statistics were used to analyse clinical and anamnestic parameters. Continuous variables were summarized by the number of patients, mean, and standard deviation (SD). At baseline (T0), the severity of HS was evaluated using three distinct staging tools: the Hurley staging system, the HS-PGA, and the IHS4. The Hurley staging system enables the classification of patients into three different stages based on disease severity. The HS-PGA and IHS4 categorize disease severity based on a cumulative numerical score, classifying it as mild (total score ≤ 3), moderate (total score ranges between 4 and 10), and severe (total score ≥ 11) [16]. To confirm the efficacy of the treatment, US evaluation was conducted at baseline (T0) as well as at the follow-up examinations (T1 and T2) using the SOS-HS, graded on a three-point scale [16]. Pain levels were also assessed at each time point using the VAS numerical score, ranging from 1 to 10. Pain levels data were analyzed longitudinally using the Friedman test and the VAS scores between T0 vs. T2 were analyzed using a two-tailed Wilcoxon matched-pairs signed rank test with FDR correction. The results of the clinical end points were analyzed with a Chi-square test using OpenEpi Version 3, open-source calculator RbyC. p values < 0.05 were considered statistically significant.

3 Results

A total of 32 patients were enrolled in this multicentric study: 17 patients from the HS outpatient clinics of the University of Brescia and 15 patients from the HS outpatient

clinics of the University of Florence underwent the treatment. Clinical and anamnestic data of the study population at baseline (T0) are summarized in Table 1.

The mean IHS4 score was 7.6 ± 5.0, while the mean HS-PGA was 2.81 ± 0.6. The SOS-HS score was 1 in 8 (25%) patients, 2 in 16 (50%), and 3 in 8 (25%). All patients presented bilateral lesions of similar severity. Among them, 13 patients (40.6%) were treatment naïve (never previously treated) with Hurley scores of 1 and 2 and received only topical treatments. Conversely, 19 patients (59.4%) with Hurley scores of 2 and 3 had been undergoing adalimumab treatment for at least 6 months, experiencing stable partial remission of the lesions. In Table 2, the therapeutic response of all patients to PDT and clindamycin after 6 weeks is reported. A complete, partial, or no response was observed in 13 (40.6%), 14 (43.8%), and 5 (15.6%) patients, respectively, at the body site treated with PDT alone, compared to 3 (9.4%), 16 (50.0%), and 13 (40.6%) patients treated with clindamycin. The Chi-square test showed that PDT was significantly more effective than the topical treatment with clindamycin ($p < 0.01$) (Table 2).

In the subgroup analysis of patients with severe disease receiving concurrent treatment with adalimumab, no statistically significant difference was found between PDT and topical clindamycin. However, a statistically significant difference in favour of PDT ($p < 0.05$) was observed in treatment-naïve patients with a milder form of the disease who received only topical treatments (Table 3).

Furthermore, the improvement in pain, measured by the VAS pain scale, was more pronounced and occurred more rapidly in patients treated with PDT (Fig. 3 and Table 4).

Both treatments were well tolerated, with no complaints of burning or stinging sensation during or after the irradiation, and no patients requested discontinuation of treatment. Mild erythema occurred in four patients after irradiation, which spontaneously resolved within 2–3 days. The gel was easy to apply and did not leave any residue in the treated area. No adverse effects to clindamycin gel were reported. In addition, the sonographic staging of HS lesions showed an improvement with both treatments, although not statistically significant, after 6 weeks (Table 5).

Within the patient cohort ($n = 32$), the comparison at T2 of SOS-HS values between lesions treated with RLP068–PDT and those treated with clindamycin indicated a greater percentage of complete response (SOS-HS = 0) with RLP068–PDT therapy ($p < 0.01$) (Table 6). This suggests a complete absence of sonographically detectable inflammatory lesions, indicating a more favourable response to RLP068–PDT compared to topical clindamycin therapy.

Figure 4 illustrates the clinical and US evaluation of an abscess at T0 (Fig. 4a,c) and its therapeutic resolution following 6 weeks of treatment with RLP068/Cl-PDT (Fig. 4b) in a single patient. Complete clinical response was confirmed via US evaluation (Fig. 4d) after 6 weeks of treatment.

Table 2 Response to PDT and clindamycin at T2

Response to treatment	PDT *n (%)*	Clindamycin *n (%)*	*p* value
Complete response	13 (40.6%)	3 (9.4%)	$p = 0.006947$
Partial response	14 (43.8%)	16 (50.0%)	
No response	5 (15.6%)	13 (40.6%)	

4 Discussion

This study marks the initial endeavour in utilizing RLP068/Cl (ELKOFAST®, non-sterile formulation) for treating HS. The overall findings suggest that photoactivated non-sterile RLP068/Cl was more effective than topical clindamycin in managing HS patients. However, the subgroup analysis revealed significantly better results in cases of milder HS treated solely with topical treatments, whereas non-sterile RLP068/Cl and clindamycin were equally effective in patients with severe cases, suggesting that both treatments may offer comparable efficacy in managing cases with severe disease when used alongside adalimumab. Several possible explanations may account for the limited therapeutic response in more severe cases. First, the extent of anatomical damage, such as sinus tracts and deep nodules, may be so severe that it becomes challenging to accurately assess clinical response. Additionally, the penetration of RLP068, as well as clindamycin, might be insufficient to

Table 3 Treatment outcomes in the subgroup of patients with more severe disease concurrently treated with adalimumab, and patients with milder disease treated with topical treatments

	Type of topical treatments	Complete response *n (%)*	Partial response *n (%)*	No response *n (%)*	*p* value
Local treatments + adalimumab ($n = 19$)	PDT	4 (21.0%)	11 (58.0%)	4 (21.0%)	$p = 0.3257$
	Clindamycin	1 (5.0%)	12 (63.0%)	6 (32.0%)	
Topical treatments only ($n = 13$)	PDT	9 (69.0%)	3 (23.0%)	1 (8.0%)	$p = 0.01058$
	Clindamycin	2 (16.0%)	4 (30.0%)	7 (54.0%)	

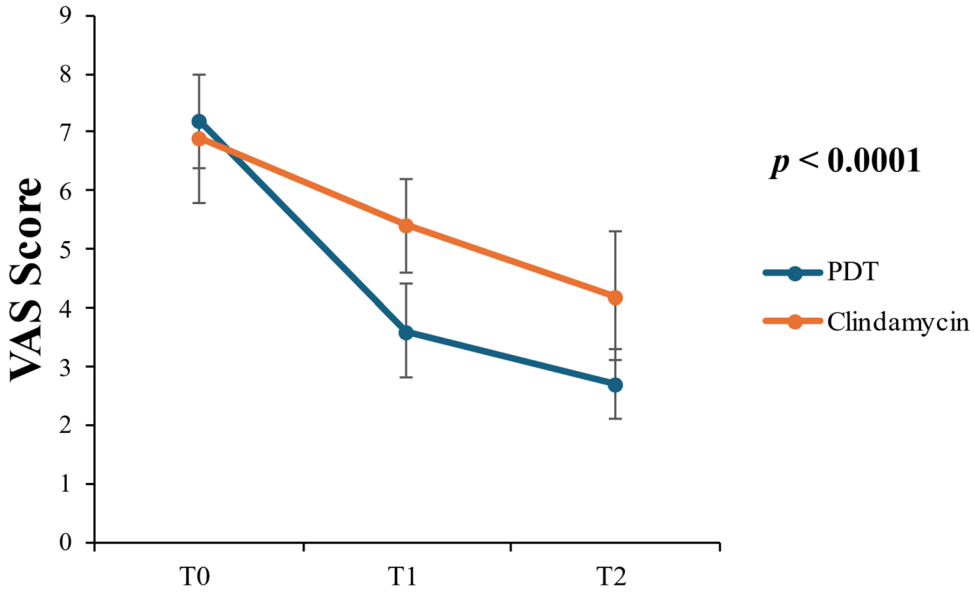


Fig. 3 The VAS pain scores during PDT and clindamycin treatments at baseline (T0), after 3 weeks (T1) and after 6 weeks of treatments (T2). The plot reports the *p* value of the Friedman test, used to assess the effect of each treatment on the VAS score ($p < 0.0001$)

Table 4 VAS pain score of the patients at baseline (T0), after 3 weeks (T1) and after 6 weeks (T2) of treatments

Type of topical treatments	T0 (mean ± SD)	T1 (mean ± SD)	T2 (mean ± SD)	*p* value (T0 vs. T2)
PDT	7.2 ± 0.8	3.6 ± 0.8	2.7 ± 0.6	$p = 1.8626 \times 10^{-09}$
Clindamycin	6.9 ± 1.1	5.4 ± 0.8	4.2 ± 1.1	$p = 2.0580 \times 10^{-06}$

p values represent the significance of differences between T0 and T2 for each treatment calculated with the Wilcoxon matched-pairs signed rank test

Table 5 SOS-HS at baseline (T0) and after 6 weeks of treatments (T2)

SOS-HS	T0, *n (%)*	T2, *n (%)*	*p* value
[1]	8 (25.0%)	15 (46.9%)	$p = 0.1515$
[2]	16 (50.0%)	13 (40.6%)	
[3]	8 (25.0%)	4 (33.3%)	

Table 6 Comparison of SOS-HS values after 6 weeks of treatments (T2) between RLP068–PDT and clindamycin treatments

SOS-HS	Post-PDT, *n (%)*	Post-clindamycin, *n (%)*	*p* value
[0]	13 (40.6%)	2 (6.2%)	$p = 0.008112$
[1]	8 (25.0%)	15 (46.8%)	
[2]	8 (25.0%)	8 (25.0%)	
[3]	3 (9.3%)	7 (21.8%)	

reach therapeutic levels in the deeper sinus tracts and nodules. Furthermore, the 630 nm light used in the treatment may not penetrate deeply enough to effectively target these areas. Employing longer wavelengths could potentially enhance treatment efficacy by improving penetration into deeper tissues. Nevertheless, it was observed that lesion improvement and pain relief were more rapid in patients undergoing RLP068/Cl-PDT treatment, compared with topical antibiotic therapy. PDT has shown potential as a monotherapy; however, the most promising outcomes are seen when combined with other treatments, including surgery. Additionally, novel intralesional delivery methods for photosensitizers have emerged as particularly effective for targeting HS lesions, improving overall therapeutic results [19]. However, the mechanisms of action remain to be fully elucidated. Some in vitro and in vivo studies demonstrated that RLP068/Cl was significantly efficient against $Gram^+$ and $Gram^-$ bacteria, yeasts, and dermatophytes [11–13]. This effectiveness may account for its beneficial effects in treating HS, a condition in which coagulase-negative *Staphylococcus*, and potentially other bacteria such as *Corynebacterium* spp., are implicated in biofilm formation. RLP068/Cl exhibits a rapid and broad-spectrum bactericidal effect against $Gram^+$ bacteria, including both planktonic and biofilm-associated methicillin-resistant *Staphylococcus aureus* [11], as well as $Gram^-$ bactericidal and fungicidal effects [20]. Both planktonic inocula and biofilms are highly prevalent in HS lesions [21], suggesting a potential correlation between

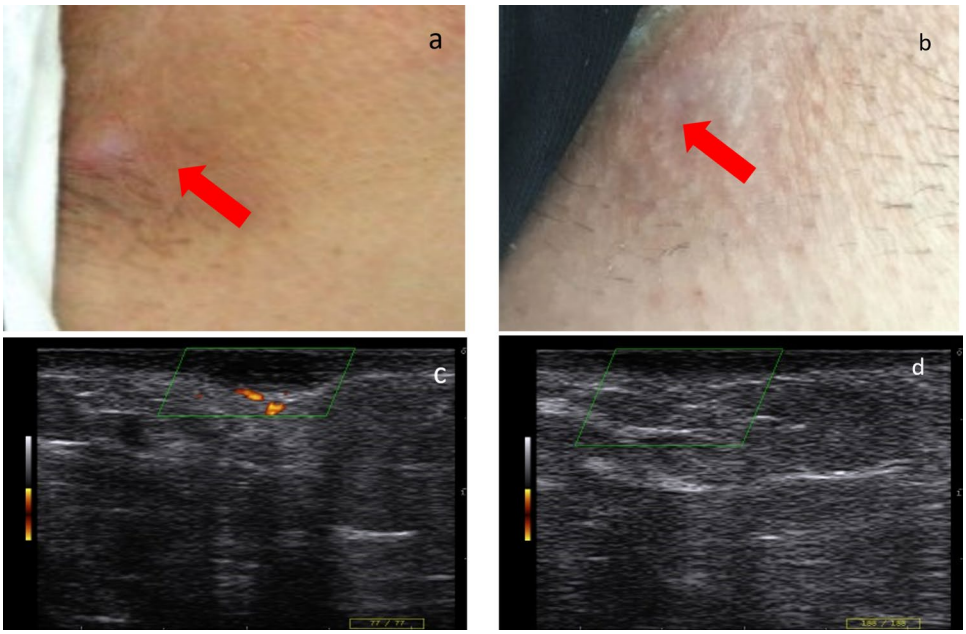


Fig. 4 Complete clinical response of an abscess after RLP068/Cl-PDT in a single patient (**a–b**), confirmed by ultrasound evaluation after 6 weeks (**c–d**)

HS and alterations in the cutaneous microbiome. The bactericidal effect may help to reduce the aberrant stimulation of the immune system, characterized by the infiltration of neutrophils, mast cells, plasma cells, and lymphocytes, as well as the hyperkeratosis of the follicular infundibulum. Moreover, due to its effects on immune and inflammatory pathways in various skin cell populations, PDT has been explored for common conditions, such as acne and photoaging but also for more challenging conditions such as *tinea capitis* [22], cutaneous mycoses [23], resistant warts, and graft-versus-host disease [24–26]. Dysbiosis of the cutaneous microbiome is believed to contribute to the pathogenesis of inflammation in HS by triggering an aberrant immune response rather than a response to an infectious process [21, 27]. Moreover, sites of biofilm formation have been found to exhibit elevated levels of $CD4^+$ T cells, which have been proposed to stimulate the production of regulatory T cells, thereby contributing to skin dysbiosis [27]. Considering the numerous intracellular targets of RLP068/Cl and its rapid action, it is conceivable that PDT may help to prevent bacterial resistance. Antiseptics, such as RLP068/Cl, are substances that are applied to the skin but not absorbed significantly and which can reduce the possibility of infection. Conversely, the use of antibiotics against bacteria can lead to antibiotic resistance, a main medical concern worldwide. Resistance to antiseptics is much less frequent, and, particularly, it was not found in vitro with repeated and protracted use of RPL068 [11, 12]. Notably, RPL068 was found effective also against methicillin-resistant *Staphylococcus aureus* [12]. This is particularly significant in the treatment of HS, where there is a complex interplay between cutaneous microbiota imbalance and the development of bacterial resistance due to topical and systemic antibiotic therapy [28]. Indeed, Bettoli and colleagues have shown a high prevalence of resistance to clindamycin (65.7%) and tetracycline (84.7%) in HS patients [29]. One of the key strategies of antibiotic stewardship in dermatology involves exploring alternatives to antimicrobial agents [20]. In this context, as evidenced by several studies, PDT could represent a promising therapeutic avenue for HS patients [8, 15, 30–33]. Consistent with this assertion, the present results show a higher rate of complete response, characterized by the absence of sonographically detectable inflammatory lesions, with non-sterile RLP068–PDT therapy compared to topical clindamycin treatment. Moreover, in terms of safety, these findings demonstrate that RLP068/Cl-PDT is consistently well tolerated, with no observed skin inflammation, and no systemic extracutaneous adverse effects, consistent with existing literature [18]. RLP068/Cl does not penetrate keratinocytes, and topical application does not lead to transcutaneous penetration into subepidermal tissues or systemic circulation [14, 15], showing high safety profiles locally and systemically, in alignment with results from in vivo experiments [12, 13]. Other photosensitizers have been previously investigated for PDT in HS [31, 33, 34]. Many studies have focused on the use of topical or intralesional methyl aminolevulinate (MAL) or aminolevulinic acid (ALA) activated by different light sources, including blue light, red light, or laser diodes [8]. MAL and ALA serve as biological precursors of protoporphyrin IX (PpIX), which is synthesized and accumulated within human and bacterial cells. Upon photoactivation, PpIX induces lethal, necrotic, or apoptotic damage [35, 36]. The mechanisms of action of blue and red-light ALA- or MAL-PDT in HS may involve their bactericidal

effects against Gram$^+$ bacteria, including *Cutibacterium acnes* and *Staphylococcus aureus*, in planktonic cultures [37, 38]. However, studies examining their activity against biofilms, especially antibiotic-resistant strains of *Staphylococcus aureus* and *Staphylococcus epidermidis*, have yielded conflicting results, with both positive and negative outcomes [37, 39–42]. Analogously, findings on Gram$^-$ bacteria (i.e. *Pseudomonas aeruginosa* and *Escherichia coli*) are inconsistent [40]. Microscopy studies have revealed that porphyrins are not localized within the envelopes of Gram$^-$ bacteria, suggesting that endogenous porphyrins may fail to target these structures [40]. Unlike RLP068/Cl-PDT, the photosensitization of epidermal keratinocytes and sebaceous glands could contribute to the therapeutic effect of ALA/MAL-PDT in HS. However, this process is also responsible for the inflammatory reaction often observed [38].

A recent meta-analysis compared blue-light PDT with ALA and red-light PDT using MAL, finding both effective but with low-quality evidence (Grade C, recommendation strength level III) due to study design limitations and bias [8]. Conversely, ALA/MAL-PDT with a 630 nm intralesional diode showed higher-quality evidence and recommendation strength (Grade B, recommendation strength level II/III). It has been hypothesized that this treatment modality may reduce inflammation via selective photo-thermolysis targeting either the blood vessels or hair follicles [43–45]. Another photosensitizer, methylene blue (MB), a cationic phenothiazinium salt, non-toxic in humans, is capable of inactivating both Gram$^+$ and Gram$^-$ bacteria [46], and eradicating various types of bacterial biofilms in vitro [47]. MB is a hydrophobic and cationic dye prone to aggregation and dimer formation, which contribute to its low phototoxicity [48]. In a pilot study involving 7 patients treated with one or two sessions of MB application and irradiation with a 635 nm light-emitting diode (LED) light, a positive response was observed in 6 patients after one-month follow-up, with 5 patients maintaining remission after six months [10]. More recently, a study of 41 patients treated with intralesional MB and LED lamp showed that over 58.5% of cystic lesions had a diameter reduction of $\geq$ 75%, with 22% showing a reduction between 50 and 75%, and 19.5% exhibiting a reduction of $<$ 50%. The recurrence rate was 12.5% [33]. Another study using a 630 nm intense pulsed light (IPL) found that topical MB in niosomes was more effective than free MB in reducing HS lesions due to enhanced drug penetration into the dermis, as the IPL filter activated MB and facilitated hair follicle destruction [9]. Another aspect worth discussing among the various treatment modalities involving these photosensitizers is the incubation time for HS. ALA and MAL creams are applied for 3–4 h under occlusive medication, followed by irradiation for 8 min with red light [34]. Alternatively, ALA and MAL creams can be used with an incubation time of 30 min, followed by irradiation with full-spectrum visible light for 2 h [49]. Conversely, MB cream and RLP068/Cl gel require 15 and 30 min, respectively, for absorption. The drug-to-light interval of conventional PDT with ALA and MAL is longer because they are prodrugs that need to be metabolized to PpIX, and the process needs time before achieving the maximal intracellular concentration of PpIX. In contrast to RLP068/Cl gel, the use of ALA and MAL gels for HS treatment is currently off-label, necessitating approval from ethical committees. Therefore, the choice between ALA, MAL, MB, and RLP068/Cl can influence the practicality and effectiveness of PDT on HS, highlighting the importance of considering all aspects of treatment in procedure planning and patient management.

5 Conclusion

In conclusion, HS is a chronic, recurrent, and debilitating inflammatory skin condition. With various treatment options available, individualized approaches are essential. Red-light PDT with RLP068/Cl (ELKOFAST®, non-sterile formulation) emerges as a promising adjunctive therapy, showing higher efficacy compared to topical clindamycin, especially in patients with mild disease (Hurley I and II stages), along with a notable reduction in pain. Nevertheless, the study has certain limitations that should be acknowledged, including the relatively small sample size, the lack of long-term follow-up to evaluate recurrence rates, and the exclusion of patients with comorbidities that could potentially affect HS severity. Future research directions should consider incorporating larger patient populations and extended follow-up periods to better assess long-term outcomes, recurrence rates, and the overall durability of the treatment effect. Furthermore, combination therapies, such as PDT alongside systemic treatments like adalimumab, could offer enhanced treatment outcomes, particularly for severe HS cases. Trials exploring such combination approaches, as well as studies comparing RLP068/Cl-PDT with other photosensitizers like ALA, MAL, and MB, will provide more comprehensive insights into optimizing PDT for HS treatment. Investigating the potential of red-light therapy alone could also shed light on the specific contributions of the light source itself in improving clinical outcomes. Overall, this study underscores the potential of RLP068/Cl-PDT as a valuable addition to the therapeutic arsenal for HS, offering hope for better outcomes and improved QoL for affected individuals.

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Data availability All data are available from the corresponding author upon request.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All subjects provided written informed consent for inclusion before they participated in the study. This study was conducted in accordance with the Declaration of Helsinki of 1975 (as revised in 2013), and the protocol was reviewed and approved by the Ethics Committee of Azienda USL Toscana Centro, Firenze (project or protocol identification number HS_R-Version 1.0 and date of approval 24th March 2021).

Informed consent All subjects provided written informed consent for inclusion before they participated in the study.

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