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Home- vs clinic-based daylight photodynamic therapy with 5-aminolevulinic acid nanoemulsion (BF-200 ALA) for actinic keratosis: A randomized, single-blind, prospective study

S. Saenz-Guirado [a,*], A Ayen-Rodriguez [a], M Galvez-Moreno [a], JP Velasco-Amador [a], JM Llamas-Molina [a], R Ruiz-Villaverde [a,b], A Molina-Leyva [b,c,d]

[a] Department of Dermatology, University Hospital San Cecilio, Granada, Spain
[b] Biosanitary Institute of Granada, IBS, Granada, Spain
[c] Department of Dermatology, University Hospital Virgen de las Nieves, Granada. Spain
[d] Facultad de Medicina. Universidad de Granada, Spain

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ABSTRACT

Background: Daylight photodynamic therapy (DL-PDT) has become one of the most effective treatments for the resolution of actinic keratosis (AK) of Olsen grade 1 and 2. Generally, PDT it is carried out in a clinic setting, which involves the patient's and their caregivers commuting to the hospital as well as a significant use of resources to carry it out within the clinic setting.
Objectives: To determine the efficacy and safety of a home-based treatment of AK with DL-PDT with the BF-200 ALA gel compared to a clinic-based setting.
Methods: The study was performed as a randomized, single-center, non-inferiority clinical trial with two parallel groups. 9 patients received one clinic-based DL-PDT (group 1) and 11 patients received one session of home-based DL-PDT (group 2). The primary endpoints were the mean AK clearance per patient and the total AK lesion clearance rate 12 weeks after treatment. The secondary endpoints were the number of remaining AKs and new AKs appearing in the treatment field 12 weeks after one PDT session. The pain during and 24 h after PDT as well as the local skin reactions were also assessed.
Results: The overall reduction of AK lesions per patient was similar in both groups with one PDT session. An overall AK clearance per patient of 10 ± 4.33 for group 1 versus 9.73 ± 2.9 for group 2 without statistically significant differences ($p = 0.868$). Regarding the clearance rate, although it was slightly higher in group 2 (71.58 ± 22.51 vs 82.1 ± 11.13), the analysis did not show statistically significant differences. The mild pain recorded during the treatment course and the mild local skin reactions were similar in both groups. Patient satisfaction was high for both groups without statistically significant differences.
Conclusion: Self-performed home-based DL-PDT with BF-200 ALA gel is as effective as the one performed in a clinic-based setting, with a comparable safety profile, high levels of patient satisfaction and with advantages for the patients and their caregivers that can enhance patient's adherence to the treatment

1. Introduction

Actinic keratoses (AKs) are common precancerous skin lesions that arise in chronically sun damaged skin. In fact, actinic keratosis (AK) is the most frequent dermatological diagnosis in Spain, followed by basal cell carcinoma [1]. At 5 years, the absolute risk of any skin cancer in patients with at least one actinic keratosis was 28.5 %. The relative risk of skin cancer overall, and specifically the risk of squamous cell carcinoma, basal cell carcinoma, and melanoma, was increased in patients with actinic keratosis [2]. The updated global prevalence of this pathology worldwide is currently 14 % and show an increasing tendency [3].

Photodynamic therapy (PDT) is a treatment that involves the use of a light-sensitive prodrug which is converted to the photosensitizer protoporphyrin IX (PpIX) which preferentially accumulates in neoplastic cells. In the presence of a light with a specific wavelength and oxygen,

* Corresponding author.
E-mail address: ssguirado@gmail.com (S. Saenz-Guirado).

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PpIX is excited and induces the destruction of neoplastic cells via apoptosis and necrosis. PDT can be administered in two ways: conventional red-light PDT, which involves a red-light lamp, and daylight PDT.

This treatment is normally performed at the clinic; however, a fully home-based PDT was previously reported which can be an option for certain medical conditions and patients [4,5].

A fully home-based PDT will allow patients to manage the skin preparation, prodrug administration and light exposure stages themselves, or by a caregiver without medical supervision. Another important aspect is that this treatment modality will provide flexibility as to when to perform the PDT. However, the efficacy maintenance and safety profile when compared to the clinical setting has not yet been reported.

2. Materials and methods

2.1. Design

A prospective, randomised, single-blind, prospective, non-inferiority clinical trial was conducted at the Dermatology Department of the Hospital Universitario San Cecilio in Granada, between July 2022 and July 2023. Patients were randomised into two parallel groups. Both groups were treated with a single session of natural DL-PDT, using BF-200 ALA gel, a 7.8 % aminolevulinic acid gel (Ameluz®, Biofrontera), as a PDT prodrug. Patients in group 1 received the treatment in a clinic-based setting, according to the Spanish-Portuguese consensus protocol for daylight photodynamic therapy [6]. Patients in group 2 were self-treated at home. These patients or their caregivers were explained how to perform the treatment in the consultation room, and written instructions were also provided.

The randomisation process was carried out using the Research Randomizer software, http://www.randomizer.org/, generating two balanced groups, which were assigned to groups 1 and 2. Group 1 with patients who underwent the treatment in the clinic, and group 2 with patients who underwent the home treatment. The researcher who carried out the assessment of the patients before and after the treatment, as well as the analysis of the data obtained, was not aware about which patient belonged to which group until the end of the study.

This study was approved by the hospital ethics committee prior to the study start (HUSC-DER_001–2022). Informed consent was signed by all patients included in the study. A flow chart of the study is available (Fig. 1).

The primary endpoints were the overall reduction in AK numbers per patients and the lesion clearance rate 12 weeks after PDT [7].

The secondary endpoints were the count in both groups of persistent lesions 12 weeks after treatment and the count of new lesions not present at the initial patient assessment.

2.2. Study population

Inclusion criteria: Patients above 18 years old, with at least 5 AK lesions of Olsen grade 1 and grade 2 [8], Olsen grading used on the single AKs, located in a single area, either the scalp, the cheek or forehead areas. In those patients who had grade 3 lesions, these were treated prior to the d-PDT session.

Excluding criteria: Patients with diffuse involvement of these areas which made it difficult to count lesions, patients with a previous AK treatment (within the previous 3 months), patients under immunosuppression, pregnancy and lactation, photodermatosis or intolerance to BF-200 ALA gel were excluded from the study.

2.3. Treatment protocol

Diagnosis was performed via clinical examination and in cases of doubt, dermoscopy was used, which has shown a sensitivity and specificity over 95 % in several studies [9,10]. Lesions were marked on a transparent plastic film, using different colours for grade 1 lesions

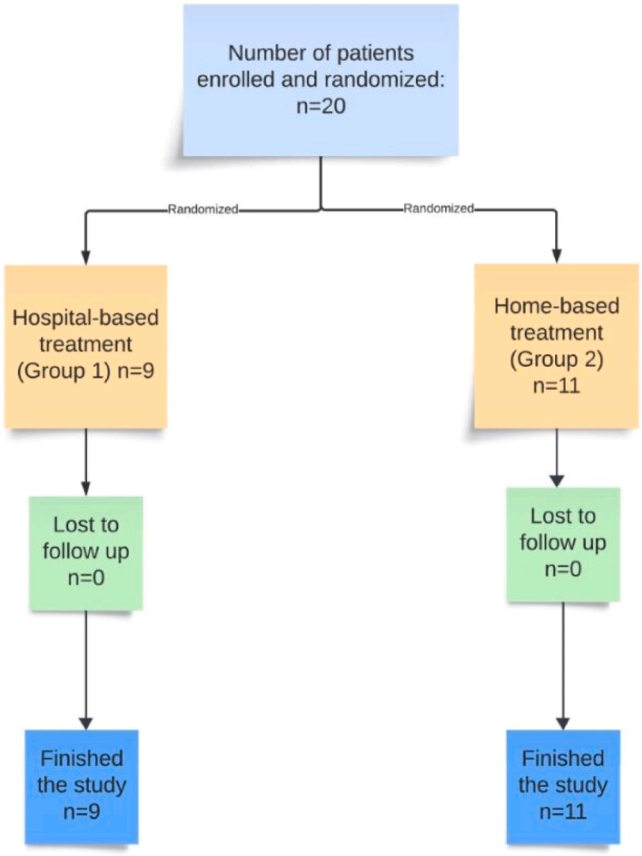

Fig. 1. Flow chart of the present study.

(black) and grade 2 lesions (red). Blue lines were drawn to mark different anatomic references, to make the evaluation of the lesions easier in the follow up appointment in the clinic at 12 weeks. That mapping was performed in the clinic by the dermatologists before the treatment. They were drawn during the first visit where the patient received the protocol information and the area that should be treated. The lesion area and therefore the treatment area was explained to the patient in the clinic prior to the treatment execution. Likewise, all treated areas were photographed before and after treatment (Fig. 2).

Grade 3 AKs were treated with 2 cycles of 10 second cryotherapy in the first consultation, prior to the treatment start. The patients were instructed to start applying 10 % salicylic petrolatum when the burnt areas were healed.

All patients in both groups were instructed to apply 10 % salicylic petrolatum once a day for a total of one week prior to the treatment in the affected area, in order to eliminate the hyperkeratosis present in some lesions. No curettage was performed prior to the application of BF-200 ALA gel on the day of treatment [11].

On the day of the treatment, BF-200 ALA was applied in a thin layer to the treatment area and patients were instructed to go out to the daylight within the first 30 min after the application of the gel. After an illumination phase of 2 h, the gel was removed. Patients were instructed to avoid sun exposure during the 48 h after treatment, the use of photoprotection and the usage of physical barriers, such as hats, were encouraged.

24 h after treatment, a telephone survey was conducted with all patients to assess the local skin reactions. Using a photographic guide, patients were asked to rate the presence of erythema, oedema, crusting, using a Likert scale from 0 to 3, where 0 meant the absence of any of these symptoms, and 3 meant the highest degree of these symptoms [12]. Pain was assessed during the DL-PDT session and 24 h after by means of a Visual Analogue Scale (VAS) 1–10. All patients had an

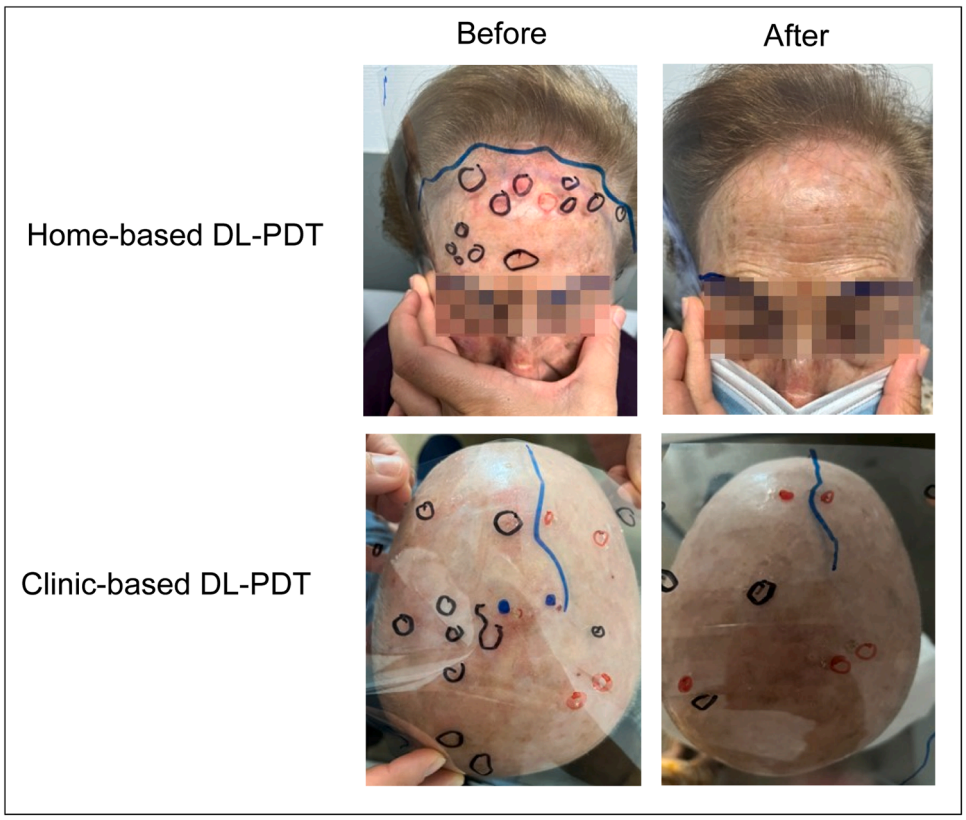

Fig. 2. Efficacy of hospital-based DL-DPT vs home-based DL-DPT 12 weeks after a single treatment session. Photographs of two patients treated with home-based DL-PDT (upper panels) and clinic-based DL-PDT (lower panels). The left panels show the baseline AK before the treatment mapped (in black grade 1 lesions and in red grade 2 lesions according to Olsen; blue lines anatomic references). The right panels show the result 12 weeks after treatment for both protocols.

appointment in the clinic one week after the treatment to evaluate the local skin reaction by means of a Likert scale from 0 to 3 for erythema, oedema and crusting (0 meant the absence of any of these symptoms, and 3 meant the highest degree of these symptoms) and the presence or absence of desquamation. Patient satisfaction was assessed 12 weeks after (VAS 1–10).

2.4. Efficacy assessment

The primary endpoints were the absolute clearance of the number of total AK, grade 1 and 2, as well as the clearance rate, considering clearance the complete disappearance of the lesion, evaluated 12 weeks after treatment by a blinded researcher [7].

The secondary endpoints were the count in both groups of persistent lesions after treatment, and the count of those new lesions, not present in the first evaluation of the patients.

2.5. Safety and tolerability assessment

Pain was assessed during the DL-PDT session and after 24 h (VAS 1–10). Local skin reactions were documented 24 h and 1 week after the treatment, and patient satisfaction was assessed 12 weeks after (VAS 1–10).

2.6. Sample size calculation

The sample size was calculated for the main study variable, reduction in the total number and percentage of grade 1 and grade 2 lesions, based on previous studies [13]. This non-inferiority study was performed, with a power of 0.90 and an alpha error of 0.05 [14], which required a total number of 194 lesions.

2.7. Statistical analysis

Statistical analysis was performed using JASP software version 0.13.1 (Amsterdam, The Netherlands). Continuous data is expressed as mean ± standard deviation. Qualitative data is expressed as percentage %. The sample was tested for normal distribution using the Shapiro-Wil test. The Student's test was applied for the analysis of continuous variables, with a 95 % confidence interval, and the Chi-square test for categorical variables. Statistical significance was considered at $p < 0.05$.

3. Results

A total of 20 patients were included in the study (19 males and 1 female, 95 % and 5 %, respectively), with a mean age of 79.25 ± 5.86. The most frequent phototype was Fitzpatrick phototype II, followed by phototype III (75 % and 25 %, respectively) with no distribution difference between the two groups. Chronic sun exposure throughout their lives was reported by 70 % of the patients, mainly for professional reasons, while the remaining 30 %, sun exposure was occasional, mainly limited to holiday periods.

A total of 255 lesions were evaluated during the study, 184 were grade 1 and 72 were grade 2 lesions (72.16 % and 27.84 %, respectively), with a similar distribution in both groups. The most frequent location of the lesions was the bald scalp. Another baseline characteristic was summarized in Table 1.

Primary endpoint: Reduction in the number of lesions and clearance rate.

Twelve weeks after treatment, the analysis of the data obtained in both groups showed no significant difference in the number of actinic keratoses cleared per patient. As such, from the initial AKs mapped, 13.56 ± 3.79 (group 1) and 12.09 ± 4.16 (group 2), a reduction of 10 ± 4.33 lesions per patient was determined in group 1 and 9.73 ± 2.9

Table 1
Patient demographics and lesion characteristics at baseline. Student's test was applied for continuous variables and Chi-square for categorical variables.

Variable	Hospital application DL-PDT $n = 9$	Home application DL-PDT $n = 11$	Total $n = 20$	P value
Sex, n (%)				
• **Male**	8 (88.9 %)	11 (100 %)	19 (95 %)	0.257[a]
• **Female**	1(11.1 %)	0	1 (5 %)	
Age (years), mean ± SD	82.67 ± 4.41	76.45 ± 5.16	79.25 ± 5.86	0.177
Fitzpatrick skin type n (%)				
• **II**	7 (77.7 %)	8 (72.27 %)	15 (75 %)	0,79[a]
• **III**	2 (22.22 %)	3 (27.27 %)	5 (25 %)	
Total lesions (%)	122(47.84 %)	133 (52.16 %)	255 (100 %)	
Total lesions grade 1 (%)	95 (51.7 %)	89 (48.31 %)	184 (72.16 %)	
Total lesions grade 2 (%)	28 (38.89 %)	44 (61.11 %)	72 (27.84 %)	
Olsen severity grading per patient, mean ± SD (range)	13.56 ± 3.79	12.09 ± 4.16	12.75± 3,96	0.425
• **Total**	10.56 ± 4.06	8.09 ± 3.7	9.2 ± 3.97	0.173
• **Grade 1**	3.11 ± 1.69	4 ± 3.26	3.6 ± 2.64	0.469
• **Grade 2**				
Localization, n (%)				
• **Scalp**	86 (70.5 %)	89 (66.92 %)	175 (68,63 %)	0.235[a]
• **Forehead**	36 (29.51 %)0	10 (7.52 %)	46 (18.04 %)	
• **Cheek**		34 (25.56 %)	34 (13.33 %)	
Sun exposure, n (%)				
• Chronic	5 (55.55 %)	9 (81.81 %)	14 (70 %)	0,202[a]
• Occasional	4 (44.44 %)	2 (18.18 %)	6 (30 %)	

DL-PDT: day light photodynamic therapy. n: number of patients; SD, standard deviation.
[a] Chi-squared test.

lesions in group 2, without statistical differences between both groups ($p = 0.868$). Analysis of the subgroups showed an AK reduction of 8.56 ± 4.42 for grade 1 lesions in group 1 vs 6.64 ± 3.07 in group 2, without statistical differences ($p = 0.098$). The same was found for Olsen grade 2 lesions (1.44 ± 1.42 in group 1 vs 3.09 ± 2.51 in group 2, $p = 0.098$, Fig. 3 and table 2).

Regarding the clearance rate, it was slightly higher in group 2, without statistically significant differences (71.58 ± 22.51 and 82.1 ± 11.13, $p = 0.191$). The analysis of the clearance rate of differentiated lesions in grade 1 and 2 in both groups was also higher in group 2, but as in the data previously reported, the differences were not significant either ($p = 0.634$ for grade lesions 1and $p = 0.029$ for grade 2 AKs, Table 2).

Secondary endpoint: Number of persistent lesions and new lesions at 12 weeks after treatment (Table 2).

At 12 weeks after treatment, the total number of permanent lesions in both groups, as well as the number of grade 1 and 2 AKs, did not show significant differences between the groups ($p = 0.237$, $p = 0.51$ and $p = 0.135$, respectively).

Regarding the number of new lesions in both groups, no significant differences were found either.

Safety and tolerability assessment and patient satisfaction (Table 3)

The pain reported by patients during the treatment was similarly low in both groups, with a mean VAS (0-[10] of 2.78 ± 2.167 in group 1 and 2.27 ± 2.37 in group 2 ($p = 0.628$). As for the pain reported 24 h after the treatment, 1.22 ± 2.33 in group 1 and 1.81 ± 1.9 in group 2 ($p =$

Table 2
Effectiveness data of Hospital application DL-PDT vs Home application DL-DPT 12 weeks after a single session of treatment.

Variable (mean ± SD)	Hospital application DL-PDT $n = 9$	Home application DL-PDT $n = 11$	P value
Overall AK reduction	10 ± 4.330	9.73 ± 2.9	0.868
Grade 1 AK reduction	8.56 ± 4.42	6.64 ± 3.07	0.268
Grade 2 AK reduction	1.44 ± 1.42	3.09± 2.51	0.098
Overall AK rate reduction%	71.58 ± 22.51	82.1 ± 11.13	0.190
Grade 1 AK rate reduction%	78.35 ± 22.46	82.44 ± 15.11	0.634
Grade 2 AK rate reduction%	48.81 ± 35.65	88.48 ± 21.78	0.029
Remaining AK	3.56 ± 2.45	2.36 ± 1.91	0.237
Remaining grade 1 AK	2. ± 1.94	1.45 ± 1.69	0.51
Remaining grade 2 AK	1.67 ± 1.11	0.91 ± 1.04	0.135
New lesions			
• **Total**	1.11 ± 1.27	0.45 ± 1.51	0.313
• **Grade 1**	0	0	0.125
• **Grade 2**	1 ± 1.12	0.27 ± 0.9	

Student's test was applied for continuous variables. DL-PDT: day light photodynamic therapy. SD, standard deviation. n, number of patients.

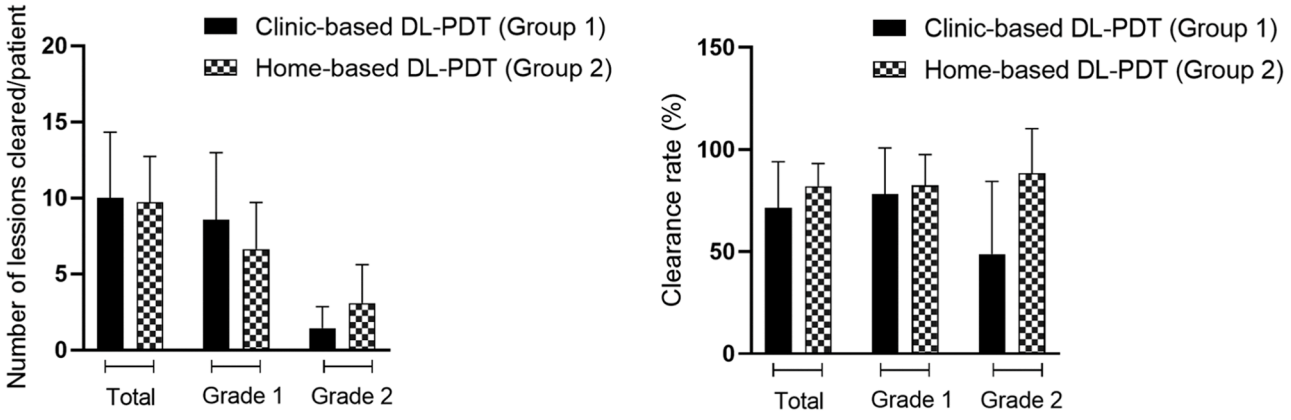

Fig. 3. Efficacy of clinic-based DL-DPT (Group 1) vs home-based DL-DPT (Group 2) 12 weeks after a single treatment session. .

Table 3
Pain during the treatment and 24 h after the treatment. Local skin reaction: 24 h and 1 week after treatment and patient satisfaction.

Variable	Hospital application DL-PDT $n = 9$	Home application DL-PDT $n = 11$	p value
Pain (1–10)	2.78 ± 2.167	2.27± 2.37	0.628
Pain (1–10) 24 h after treatment	1.22 ± 2.33	1.81 ± 1.9	0.54
Local skin reaction 24 h after treatment			
Erythema (0–3)	1.33 ± 1	1.09 ± 0.3	0.453
Edema (0–3)	0.22 ± 0.44	0.36 ± 0.5	0.518
Crusting (0–3)	0.11 ± 0.33	0.45 ± 0.52	0.105
Local skin reaction 1 week after treatment			
Erythema (0–3)	0.67 ± 0.7	0.82 ± 0.6	0.611
Edema (0–3)	0	0	
Flaking, n (%)	6 (66.67 %)	6 (54.55 %)	0.582[a]
Crust (0–3)	0.44 ± 0.73	0.36 ± 0.51	0.773
Patient satisfaction	8.67± 1.23	8.45 ± 0.93	0.440

Student's test was applied for continuous variables and Chi-square for categorical variables.
DL-PDT: day light photodynamic therapy. n: number of patients; SD, standard deviation.
[a] Chi-squared test.

0.54), respectively, also showed no differences between the two groups.

All patients in the study showed local reactions 24 h after treatment, some of which persisted up to 7 days. None of the reactions were severe enough to require any action. The most frequent was slight erythema, which was similar in both groups, both at 24 h and one week after treatment. The rest of the local skin reactions, which were of mild severity, that were evaluated also showed no differences between the two groups.

Patient satisfaction after treatment was considerably high in all patients in both groups, always above 7 on a VAS scale (0-[10], with an average of 8.667 ± 1.225 in group 1 and 8.455 ± 0.934 in group 2 (p = 0.440).

4. Discussion

Daylight photodynamic therapy is one of the most widely used treatments for AKs today due to its efficacy, tolerability and the mild local skin reaction it usually produces [15,16]. In addition, it can treat not only clinically visible lesions, but also the cancerised field where the visible lesions are located, and therefore targeting other subclinical lesions with carcinogenic potential [17].

The high prevalence of AK, especially in countries such as Spain, with a high number of hours of sunshine per year, places a high pressure on dermatology departments to properly diagnose, treat and monitor patients with AK, which is now considered a chronic disease [18].

Home-based DL-PDT can save resources for the health systems and relieve the pressure on the dermatology departments, which are currently overburdened [19,20].

Until now, DL-PDT has been carried out in the clinic setting, as it requires prior preparation of the patient, with prior curettage of the lesions, application of the drug and subsequent gel removal after the exposure to daylight. Although PDT without curettage has shown to be as effective [11], other studies showed that curettage enhanced PDT even when using BF-200 ALA or MAL [21], so we decided to apply 10 % salicylic petrolatum to enhance the PDT and also to follow as close as possible the Spanish-Portuguese daylight PDT consensus protocol where curettage is described. However, we tried to avoid the classic curettage and make the procedure as easy as possible for the patient.

However, these hours in the clinic are often inconvenient for the patients, who are usually elderly and have difficulty moving around. In addition, patients often live in areas far from the reference clinic, making the commute an extra added burden for the elders.

There are up to now two articles in the literature evaluating the efficacy of home-based DL-PDT, concluding that this treatment modality is effective and safe, with high patient satisfaction. García-Gil et al. study included 22 patients with grade 1 and 2 AK, treated with a single session of home-based DL-PDT, with a clearance rate of 65.9 % 12 months after the treatment [5]. Other study conducted by Karrer et all in Germany achieved clearance rate of 62 % in 50 patients, 12 weeks after the treatment [4].

This study, however, compares for the first time self-applied home-based DL-PDT with BF-200 ALA gel with the clinic-based DL-PDT, performed by specialised personnel, confirming that the former is at least as effective as the latter in AKs of Olsen grade 1 and 2 12 weeks after PDT. No statistically significant differences were observed in either the reduction of the absolute number of lesions or the clearance rate. There was also no difference in the number of persistent or new lesions, therefore demonstrating the same efficacy between both protocols.

Pain during treatment and local skin reaction were similar in both groups.

This study shows for the first time that, after a clear and concise explanation of how the treatment should be carried out, as well as the proper aftercare, patients are able to carry out the treatment at home, either by themselves or by their caregivers, with results similar to those obtained in previous studies of clinic-based DL-PDT.

The present study has, however, a number of limitations. Firstly, the number of lesions assessed is somewhat limited. Secondly, only the investigator who performed the first patient assessment as well as the 12-week assessment was blinded. Both the investigator who carried out the treatment on group 1 patients and the patients were not blinded for obvious reasons. Thirdly, the data corresponding to the assessment of the local reaction 24 h after treatment was determined by the patient; although patients were given photographic references to score these reactions, these data could vary due to the patients' own subjectivity. Finally, 12-week follow-up period could be considered too short.

In conclusion, this study is the first to our knowledge to demonstrate non-inferior efficacy of DL-PDT with BF-200 ALA gel self-applied by the patient at home compared to DL-PDT performed in the dermatology department by qualified personnel. The results obtained show an excellent ability of patients to perform the treatment themselves, obtaining clearance and lesion reduction rates similar to clinic-based treatment, with a good safety profile that does not differ from the clinic-based treatment and a high level of satisfaction. We believe this data, together with the increased comfort for the patient and the flexibility this new treatment modality offers will enhance patient adherence to the treatment towards enhancing prevention in the long run.

CRediT authorship contribution statement

S. Saenz-Guirado: Writing – original draft, Investigation. **A Ayen-Rodriguez:** Writing – original draft, Investigation. **M Galvez-Moreno:** Investigation. **JP Velasco-Amador:** Investigation. **JM Llamas-Molina:** Investigation. **R Ruiz-Villaverde:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation. **A Molina-Leyva:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation.

Declaration of competing interest

None

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