

ORIGINAL ARTICLES

# Retrospective, Descriptive, Observational Study of Treatment of Multiple Actinic Keratoses With Topical Methyl Aminolevulinate and Red Light: Results in Clinical Practice and Correlation With Fluorescence Imaging

M. Fernández-Guarino,<sup>a</sup> A. Harto,<sup>a</sup> M. Sánchez-Ronco,<sup>b</sup> B. Pérez-García,<sup>a</sup> A. Marquet,<sup>a</sup> and P. Jaén<sup>a</sup>

<sup>a</sup>Servicio de Dermatología, Hospital Universitario Ramón y Cajal, Universidad de Alcalá de Henares, Madrid, Spain

<sup>b</sup>Departamento de Ciencias Sanitarias y Médico-Sociales, Facultad de Medicina, Universidad de Alcalá de Henares, Madrid, Spain

**Abstract.** *Background.* Actinic keratosis (AK) is one of the most common skin diseases seen in clinical practice. In the last 5 years, several studies assessing the efficacy of photodynamic therapy in the treatment of multiple AKs have been published.

*Objective.* We aimed to assess the clinical outcomes of photodynamic therapy in patients with multiple AKs and the correlation of those outcomes with fluorescence imaging.

*Material and methods.* In this retrospective, descriptive, observational study of 57 patients treated in our hospital with photodynamic therapy for multiple AKs, we recorded age, sex, and lesion site (face, scalp, and dorsum of the hands). All patients were treated in the same way: methyl aminolevulinic acid (Metvix<sup>®</sup>) was applied for 3 hours and the skin then irradiated with red light at 630 nm, 37 J/cm<sup>2</sup>, for 7.5 minutes (Aktilite<sup>®</sup>). The response, remission duration, tolerance, number of sessions, and fluorescence images were recorded by site. The  $\chi^2$  test was used to assess between-site differences and the correlation between fluorescence imaging and clinical response.

*Results.* The greatest improvements were obtained for facial lesions; these required fewer sessions and remission lasted longer than lesions at other sites. The treatment was best tolerated on the dorsum of the hands. The fluorescence area and the reduction in intensity on applying treatment were found to be strongly and significantly correlated with the extent of clinical response.

*Conclusions.* Overall, the outcomes of treatment of multiple AKs with photodynamic therapy are better for the face than for the scalp and dorsum of the hands. Fluorescence imaging may be an effective tool for predicting response to treatment.

**Key words:** photodynamic therapy, actinic keratosis, methyl aminolevulinate, red light, fluorescence diagnosis.

## ESTUDIO RETROSPECTIVO, DESCRIPTIVO Y OBSERVACIONAL DEL TRATAMIENTO DE QUERATOSIS ACTÍNICAS MÚLTIPLES CON METILAMINOLEVULINATO TÓPICO Y LUZ ROJA: RESULTADOS EN LA PRÁCTICA CLÍNICA Y CORRELACIÓN CON LA IMAGEN DE FLUORESCENCIA

**Resumen.** *Introducción.* Las queratosis actínicas (QA) son una de las patologías cutáneas más frecuentes en la práctica clínica. En los últimos 5 años se han publicado varios estudios que evaluaban la eficacia de la terapia fotodinámica (TFD) en el tratamiento de múltiples QA.

*Objetivo.* Evaluar los resultados de la TFD de múltiples QA por localizaciones y su correlación con la imagen de fluorescencia.

*Material y métodos.* Realizamos un estudio retrospectivo, descriptivo y observacional de los pacientes tratados por múltiples QA con TFD en nuestro hospital. Se describe la edad, el sexo y la localización de las lesiones

(cara, cuero cabelludo y dorso de las manos) de los 57 pacientes. Se trató a todos los pacientes usando los mismos parámetros: ácido metilaminolevulínico (MAL, Metvix<sup>®</sup>) ocluido tres horas e irradiación con luz roja de 630 nm, 37 J/cm<sup>2</sup>, 7,5 minutos (Aktilite<sup>®</sup>). Se describe la respuesta, período de remisión, tolerancia, número de sesiones y la fluorescencia según localizaciones. Con la prueba Chi-cua-

Correspondence:  
Montse Fernández-Guarino  
Hospital Ramón y Cajal  
Carretera de Colmenar km. 9.100  
28034 Madrid, Spain  
montsefdez@msn.com

drado se evalúan las diferencias entre localizaciones y la correlación de la imagen de fluorescencia con la respuesta clínica.

*Resultados.* En la cara se obtiene mayor grado de mejoría, se requieren menor número de sesiones y mayores períodos de remisión que en el resto de las localizaciones. El dorso de las manos es la zona mejor tolerada. Existe una correlación alta y significativa entre el área de fluorescencia y su disminución al aplicar el tratamiento, con el grado de respuesta clínica.

*Conclusiones.* Los resultados en el tratamiento de múltiples QA con TFD son mejores, globalmente, en la cara que en el cuero cabelludo y en el dorso de manos. El diagnóstico de fluorescencia puede ser una herramienta eficaz para predecir la respuesta al tratamiento.

**Palabras clave:** terapia fotodinámica, queratosis actínicas, metilaminolevulinato, luz roja, diagnóstico de fluorescencia.

## Introduction

Actinic keratosis (AK) is one of the most common skin conditions observed in clinical practice. Exact prevalence varies according to geographic region, although approximately 10% are seen in patients aged 20 to 30 years, and this increases to 80% in patients aged 60 to 70 years. This condition is more common in fair-skinned patients with a history of intense exposure to sunlight. Solid organ transplant recipients and patients undergoing continuous immunosuppressive therapy have a greater risk of presenting AK.<sup>1</sup> Diagnosis is usually clinical, and it is important to treat AK because it may progress to squamous cell carcinoma, as occurs in about 8% of cases.<sup>2</sup> Given that it is impossible to predict which lesions will become invasive, many authors consider that all cases of AK should be treated. Cryotherapy is the standard treatment, although in the case of multiple keratoses, topical imiquimod or photodynamic therapy (PDT) is more appropriate.

Topical methyl aminolevulinate (MAL) or  $\delta$ -aminolevulinate ( $\delta$ -ALA) leads to an accumulation of intracellular protoporphyrin IX (ppIX), predominantly in neoplastic and preneoplastic cells. Subsequent irradiation in the porphyrin absorption spectrum generates oxygen radicals and selectively destroys target cells.<sup>1,3</sup> Fluorescence imaging involves detection of the red fluorescence emitted by the ppIX of the affected cells when the lesion is irradiated with Wood light (370–400 nm). Fluorescence is the emission of light by atoms or molecules that have been stimulated by energy absorption. MAL plays an important role in fluorescence diagnosis, as it selects neoplastic or inflammatory tissue (it is more selective than  $\delta$ -ALA).<sup>3,4</sup> Histopathology shows that more intense fluorescence correlates with a higher level of ppIX.<sup>5</sup> Irradiation with a suitable light source reduces ppIX, with a consequent loss

of fluorescence in the lesions treated, in a process known as photobleaching. The potential of fluorescence diagnosis remains unknown, not only for distinguishing the lesions, but also for determining the possible efficacy of treatment. The higher the accumulation of ppIX, that is, more intense pretreatment fluorescence, the greater the potential for tissue damage. The appearance of photobleaching after PDT points to consumption of ppIX and, therefore, tissue damage.

We review the results of treating 57 patients with multiple AKs using topical MAL and red light, and investigate the correlation between these agents and fluorescence imaging.

## Objective

To assess the clinical outcome, tolerance, and remission duration achieved with PDT in the treatment of multiple AKs according to site and the correlation between this approach and fluorescence imaging.

## Material and Methods

### Patients

We performed a retrospective, descriptive, observational study of patients treated for AK with PDT at our hospital between April 2005 and May 2007. We selected patients with more than 5 nonhypertrophic AK lesions who had not received any treatment for at least 1 month before the PDT session. Diagnosis was based on clinical criteria, and was supplemented with histology in only a few cases. At inclusion, all the patients fulfilled the criteria of the United States Food and Drug Administration (no known sensitivity



**Figure 1.** Patient referred for treatment of multiple actinic keratosis lesions on the scalp.



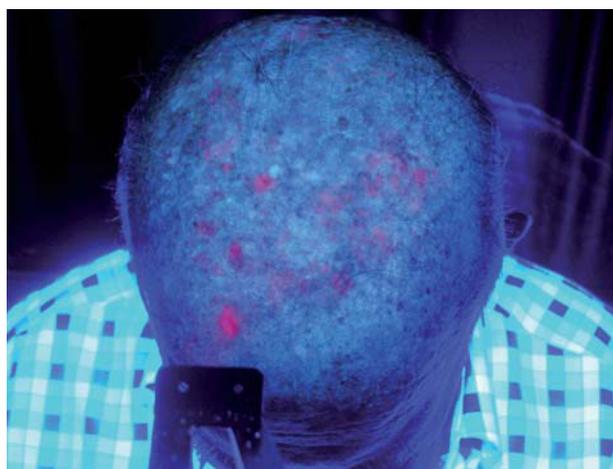
**Figure 2.** Fluorescence image. Notice how fluorescence is limited to less than 30% of the area to be treated, that is, the whole of the upper portion of the scalp.

to porphyrins or nuts; no topical corticosteroids during the preceding 2 weeks; no topical or systemic retinoids, topical hydroxy acids, chemotherapy, or immunotherapy during the preceding 4 weeks; not pregnant or breastfeeding). This subsequent review also excluded patients with pigmented lesions and those who were immunodepressed as a result of therapy or disease. All patients were given verbal and written information about the treatment they were to receive. We reported patients' age and gender, and the site of the lesions (scalp [Figure 1], face, and dorsum of the hands) treated with PDT.

## Treatment Process

Each patient was treated according to the area affected, that is, the face, the dorsum of the hands, or the upper portion of the scalp. The lesions were evaluated initially based on clinical evidence, digital photography, and fluorescence photography. The percentage of the area affected was determined visually and by palpation according to the methodology described by Olsen et al.<sup>6,9</sup> The lesions were classified in 4 grades according to the percentage of the area affected: grade 1, up to 25%; grade 2, from 25% to 50%; grade 3, from 50% to 75%; and grade 4, from 75% to 100%.

All the patients underwent the same treatment process. Before PDT was applied, the area to be treated was cleaned with saline solution and curetted if small scabs or areas of flaking were present. A 1-mm thick layer of MAL (Metvix, Galderma) was applied to the affected area, which was occluded for 3 hours using an adhesive film (Tegaderm) and covered with an opaque white dressing to prevent inactivation of MAL by visible light. After 3 hours, the occlusion was removed and the occluded area was cleaned



**Figure 3.** Fluorescence image taken before the second session. Fluorescence continues to be less than 30% of the area to be treated; therefore, no reduction in fluorescence is observed after the first session.

with saline solution. The area was irradiated immediately with red light at 630 nm (Akilite) from a distance of 5–8 cm for 7.5 min at 37 J/cm<sup>2</sup>. Just before exposure to the light, a fluorescence photograph was taken using a camera (Olympus C5060) with a 400-nm UV flash (ClearStone VD-DA digital system). Previous fluorescence of the area to be treated was also measured as a percentage of the affected area exhibiting fluorescence (Figure 2), and was classified into 3 groups by percentage of the area to be treated: group 1, up to 30%; group 2, from 30% to 70%; and group 3, from 70% to 100%. The PDT session was repeated 3 weeks later, following the same procedure (Figures 3 and 4).



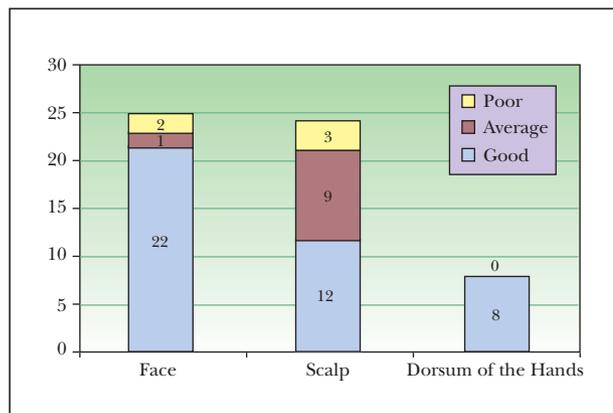
**Figure 4.** Photograph of the second session, at 3 weeks. A discreet improvement can be observed. Photodynamic therapy is reapplied.



**Figure 5.** Checkup at 3 months after the second session. A reduction of more than 50% in the area of the actinic keratosis lesions is observed; therefore, it is classified as a complete response.

### Evaluation of the Response

Patients were evaluated at 3 months and classified as having a partial response if the AK was reduced by less than 50% (1 interval in the degree of involvement) (Figure 5), and as a complete response if AK was reduced by 50% to 70% (2 intervals in the degree of involvement). Patients were monitored every 3 months. The number of sessions applied was evaluated, as was the time when new treatment—PDT or other—was indicated by the dermatologist (remission period). Pretreatment fluorescence was compared with that determined after the first session with PDT and the outcome classified as no reduction or worsening, medium reduction (1 reduction interval), and large reduction (2 reduction intervals). Adverse events other than the scabs,



**Figure 6.** Tolerance by site.

erythema, edema, or hyperpigmentation that are typical of PDT were recorded. Lastly, tolerance to treatment was described subjectively by the patient as good, average, or poor (Figure 6).

### Statistical Analysis

The distribution of variables—response, number of sessions, pretreatment and posttreatment fluorescence, and remission duration—was compared using the  $\chi^2$  test.

The correlation between pretreatment and posttreatment fluorescence, tolerance, number of sessions, and the degree of improvement was also evaluated using the  $\chi^2$  test.

### Results

The results are summarized in Table 1. The study sample included 57 patients, of whom 25 received treatment on the face, 24 on the scalp, and 8 on the dorsum of the hands. There were more men than women (50 men, 7 women). The mean age was 76.7 years, and this was higher for patients who received treatment on the dorsum of the hands and the scalp (77.1 and 75.4 years, respectively) than for those who received treatment on the face (73.4 years). Most patients (39/57) had already received treatment for AK. The mean number of sessions was 1.8 for the face, 1.9 for the scalp, and 2 for the hands, although the differences were not statistically significant. The overall outcome of treatment was a 73.1% reduction in the lesions. Remission was significantly better ( $P=.000$ ) on the face, with disappearance of 92.5% of the lesions, than at the other sites (scalp 60% and dorsum of the hands 47%) (Figure 7). The overall symptom-free period was 6.9 months. Most of the long remission periods were for the face ( $P=.004$ ), with a mean of 7.9 months (5.8 months for the scalp and 6.8 months for the dorsum of the hands). Overall, the

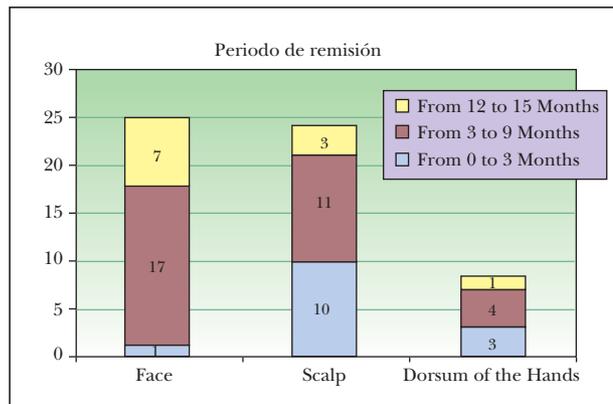
**Table 1.** Patient Characteristics

	Face	Scalp	Dorsum of the Hands	Total (N=57)
Number of patients	25	24	8	57
Gender	4 W/21 M	1 W/23 M	2 W/6 M	7 W/50 M
Mean age (range), y	73.4	75.4	77.1	74.6 (60-95)
Previous treatment	14 cryotherapy 1 cryotherapy and imiquimod 10 none	16 cryotherapy 8 none	8 cryotherapy	38 cryotherapy 1 cryotherapy and imiquimod 18 none
Number of sessions	1.8	1.9	2	1.9 ( $P=.688$ )
Degree of improvement	92.50%	60%	47.50%	73.1% ( $P=.000$ )
Duration of remission	7.9 months	5.8 months	6.8 months	6.9 months ( $P=.004$ )
Tolerance	22 good (88%) 1 average (4%) 2 poor (8%)	12 good (50%) 9 average (37%) 3 poor (13%)	8 good (100%)	42 good (74%) ( $P=.008$ ) 10 average (18%) 5 poor (8%)
Pretreatment fluorescence	75.50%	62.10%	25.10%	62.3% ( $P=.000$ )
Posttreatment fluorescence	51.20%	50.70%	16%	46% ( $P=.000$ )
Difference in fluorescence area	24.30%	11.40%	9.10%	16.3% ( $P=.075$ )

Abbreviations: M, man; W, woman.

treatment was well tolerated; 74% of the patients reported that tolerance was good. The correlation between tolerance and statistical significance was high and significant ( $P=.008$ )—all patients reported good tolerance for the dorsum of the hand and there was a high percentage of good tolerance for the face (88%). Pretreatment fluorescence was not randomly distributed at each site ( $P=.000$ ), as it was more common on the face (75.5%) and the scalp (62.1%) than on the dorsum of the hands (25.1%). Posttreatment fluorescence also varied significantly according to the site ( $P=.000$ )—it was also greater for the face and scalp (51.2% and 50.7%, respectively) than for the dorsum of the hands (16%). The reduction in the fluorescence area after treatment was 24.3%, 11.4%, and 9.1% on the face, scalp, and dorsum of the hands, respectively. Fluorescence did not vary significantly by site ( $P=.075$ ).

There was a high and significant correlation ( $P=.008$ ) between the fluorescence area before treatment and the number of patients who obtained complete remission (Table 2). Thus, 75% of patients with complete responses presented high fluorescence (71%–100% of the area treated), and 75% of the patients with partial responses presented low fluorescence (0%–30% of the area treated). The reduction in fluorescence after the PDT session also correlated strongly and significantly with a better response to treatment. Most patients with medium (68.4%) and high (75%) reductions had complete responses.



**Figure 7.** Remission period by site.

## Discussion

PDT is effective, safe, and well tolerated, and has an excellent cosmetic outcome in the treatment of AK. Its main advantage is the ability to treat several lesions simultaneously, at both the clinical and the subclinical level, since it acts directly on cells. Recent studies on PDT in dermatology have shown promising results and progress continues to be made, both for approved indications (AK, basal cell epithelioma, and Bowen disease) and for off-label indications.<sup>7</sup>

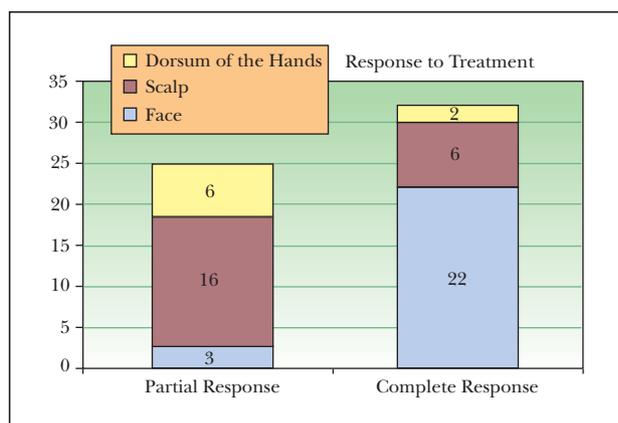
**Table 2.** Correlation of the Response With Pretreatment Fluorescence and With Reduced Use of This Therapy

	Response		P ( $\chi^2$ )
	Partial Response	Complete Response	
<i>Pretreatment fluorescence</i>			
0% to 30%	9 (75%)	3 (25%)	P=.008
31% to 70%	11 (50%)	11 (50%)	
71% to 100%	5 (27.7%)	18 (75%)	
<i>Reduction in fluorescence</i>			
No reduction or condition worsens	14 (77.8%)	4 (22.2%)	P=.002
Medium reduction	6 (31.6%)	13 (68.4%)	
High reduction	5 (25%)	15 (75%)	

**Table 3.** Published Studies That Evaluate the Efficacy of Photodynamic Therapy With 3-Hour Methyl Aminolevulinic Acid and Red Light in the Treatment of Actinic Keratosis

Study	Design	Number of Patients <sup>a</sup>	Number of Treatments	Follow-Up Period	Results
Szeimies <sup>9</sup> 2002	PDT compared with cryotherapy	102	1	3 months	CR: 69% of lesions Better cosmetic response with PDT
Freeman <sup>12</sup> 2003	PDT compared with cryotherapy and compared with placebo	88	2	3 months	CR: 91% of lesions Better cosmetic response with PDT
Pariser <sup>10</sup> 2003	PDT compared with placebo	42	2	3 months	CR: 89% of lesions
Tarstedt <sup>8</sup> 2005	PDT	106	1 compared with 2	3 months	CR: 81% in 1 session CR: 87% in 2 sessions
Morton <sup>11</sup> 2006	PDT compared with cryotherapy	119	2	6 months	CR: 86% of lesions

<sup>a</sup>Number of patients from the group treated with photodynamic therapy. Abbreviations: CR, complete remission; PDT, photodynamic therapy.



**Figure 8.** Response to treatment by site.

The studies published to date on treatment of multiple AKs using MAL and red light are prospective, randomized, controlled studies with a well-defined follow-up period

(Table 3). The primary objective of our study was different, since it retrospectively described the result of treating AK with PDT in clinical practice. Therefore, we evaluated patients not by the total number of lesions, but by the lesions at each site, in an attempt to use a more practical approach. Previous case series treated each lesion individually and counted them one by one. We treated our patients by site, since the light source allows us to do this in daily clinical practice. We then evaluated the response according to the percentage reduction in the number of AKs at each site (Figure 8). This practice enables us to eliminate subclinical lesions and to improve the clinical diagnosis using the fluorescence techniques. This is the first study of PDT in the treatment of AK to evaluate the correlation between the fluorescence of the lesions and the response to treatment.

We selected patients with several nonhypertrophic AK lesions (more than 5), as, in principle, they were ideal candidates for this technique. Using this criterion, we observed a higher number of men (50/57, 88%) and elderly

patients (mean age in each of the 3 groups, 74.6 years). The direct relationship between AK and accumulated exposure to sunlight explains why patients were elderly and more frequently men. Work in the open air and greater frequency of alopecia leaving the scalp unprotected is responsible for men being more exposed to sunlight than women throughout life. We considered AK independently of gender. Previous studies included a similar number of men and women, and revealed no statistically significant differences between them.<sup>3-5,6</sup> The study by Morton et al,<sup>11</sup> which was similar to ours, analyzed a sample of which 91% were men.

Most of the patients who received PDT (39/57, 68%) had already received cryotherapy, revealing that PDT is not usually the first choice of technique. Given its accessibility and ease of use, cryotherapy is generally the dermatologist's preference. PDT tends to be considered an option when cryotherapy fails or there are several lesions.

Previous studies using MAL-PDT to treat AK (Table 3) compare the efficacy of 1 and 2 sessions,<sup>8</sup> or treat all patients with 2 sessions,<sup>9-11</sup> since this regimen has proven to be more effective. We take the opposite approach, that is, the dermatologist performs as many sessions as he or she considers necessary to obtain a suitable clinical response. The group mean was 1.9 sessions (1.8 for the face, 1.9 for the scalp, and 2 for the dorsum of the hands). Therefore, a mean of 2 sessions was not reached. This is so because the dermatologist considered it unnecessary to have a second session in the case of patients with an excellent response, and such responses are more frequent on the face than the scalp. It was not the case for the dorsum of the hands in any of our patients. However, these differences are not statistically significant; therefore, in retrospect, the ideal regimen is 2 sessions for all sites, thus confirming the standard of care.

The complete response for the group was 73.1%, which is similar to the percentage observed by Szeimies<sup>9</sup> (69%). Nevertheless, these results are lower than those of other studies (81%-91%).<sup>8,10-12</sup> This lower overall response may be due to the fact that we included the dorsum of the hands, a site with worse response (47.5%), whereas all the previous studies are limited to the face and scalp. If we excluded the dorsum of the hands from our analysis, the percentage of cure would be 77%, that is, closer to the results of previous studies. If we compare these results with those of cryotherapy, they are quite similar (68%-72%).<sup>11,12</sup> However, in most of our patients, this treatment had already been applied and we opted to administer PDT afterwards, perhaps due to the lack of response to cryotherapy, the presence of multiple lesions, or the search for better cosmetic results.

The results of treating AK on the face were excellent (92% response rate), somewhat better than on the scalp and dorsum of the hands (60% and 47.5%, respectively). This difference was very significant ( $P=.000$ ). Therefore, our results show that PDT is most effective on the face, then on the scalp, and lastly on the dorsum of the hands.

These findings are logical if we consider that the thickness of the lesions is fundamental in this technique and that AKs on the face generally tend to be less hypertrophic than on the scalp and dorsum of the hands. Published studies on MAL-TFD do not evaluate lesions by site, and only Morton<sup>11</sup> reports response rates on the face and scalp. At 3 months, the rates of cure were 84%-91% for the face and 81%-84% for the scalp. At 6 months, the response rates were 89%-92% for the face and 83%-84% for the scalp. As observed, the results are better on the face, and the percentages are similar to those found in our study. However, the study does not analyze whether these differences were statistically significant or not, since the objective was to compare PDT with cryotherapy.

A fundamental aspect of clinical practice is the amount of time patients remain free of treatment, whether PDT or any other treatment for AK. The mean treatment-free period was 6.9 months and, again, logically, better results were obtained for the face, with a mean remission of 7.9 months ( $P=.004$ ). Previous randomized studies have shorter follow-up periods (3 months<sup>8-10</sup>), except that by Morton.<sup>11</sup> The poorest results may be due to the fact that the patients were followed for longer. Therefore, if they had been evaluated at 3 or at 6 months, the clinical response at that time would probably have been better, since the decision to re-treat was not taken until a mean of 6.9 months later. In other words, the patient was not treated earlier, probably because it was not necessary.

In subjective terms, 74% of patients felt that PDT was well tolerated. If we analyze the data by site, treatment was worst tolerated on the scalp (approximately only half of patients tolerated sessions well,  $P=.008$ ). Therefore, the scalp generally required analgesic measures (humidification, treatment interruptions) more often than the other sites. Tolerance was excellent on the hands—all patients tolerated it well—and on the face, where 88% also tolerated it well. One previous study compared the tolerability of PDT with that of cryotherapy and found that patients tolerated PDT better.<sup>9</sup>

Application of topical MAL leads to accumulation of ppIX in neoplastic and preneoplastic cells. Fluorescence diagnosis can detect this accumulation using UV light (Wood light), which reveals those cells that have the potential to be destroyed by PDT. It therefore seems logical to think that this correlates with the ability to obtain a better response to treatment.<sup>1,3</sup> Ours is the first study in the literature to evaluate this correlation. It was measured in the same way as the lesions, that is, by the percentage of area to be treated that exhibited red fluorescence. Nevertheless, this is a difficult parameter to evaluate and, in the future, it might be determined using digital photography. We observed that fluorescence was not randomly distributed, but that pretreatment and posttreatment fluorescence was significantly more intense on the face than on the scalp and

the dorsum of the hands. ( $P=0.000$ ). This may have several explanations. First, the endogenous fluorescence of *Propionibacterium acnes* is more intense in seborrheic areas (face). Second, facial lesions are less hyperkeratotic and MAL penetrates AK more easily. Lastly, the more intense inflammation in the facial lesions makes them more fluorescent. Whatever the cause, for practical purposes, pretreatment fluorescence and its reduction on irradiation with red light correlate strongly with clinical response ( $P=0.008$  and  $P=0.002$ , respectively). Thus, 75% of patients with a complete response had fluorescence on more than 70% of the area to be treated (Table 2). On the contrary, most patients with partial responses (75%) had fluorescence in less than 30% of the area to be treated. The reduction in fluorescence also seems to be an important parameter when predicting the response to treatment. Thus, 75% of patients with high reductions presented a complete response, compared with 22% of those with nonreductions or exacerbations.

Our review of the literature revealed only 1 study that evaluated fluorescence diagnosis in the treatment of multiple AKs (37 patients),<sup>13</sup> although it did so using  $\delta$ -ALA as a photosensitizer instead of MAL; therefore, it is not completely comparable with our study. MAL produces more selective fluorescence than  $\delta$ -ALA; therefore, in principle, its greater accuracy makes it more indicated for fluorescence diagnosis.<sup>5</sup> The study in question aimed to vary the intensity and wavelength of different light sources to achieve photobleaching of the AK and thus determine whether a better response could be obtained. The idea of reducing fluorescence by exhausting it with a light source is common to both studies; however, in the strict sense, the study is different from ours, not only in terms of the photosensitizer used. We part from the response to fluorescence and we do not vary the fluence or the wavelength; by contrast, the authors of the other study work in the opposite direction, by exhausting fluorescence with different fluence levels before examining the response. Nevertheless, they found, as did we, that a greater rate of initial fluorescence and photobleaching correlated with a better response by the AK. They evaluated patients at 7 weeks of treatment but did not follow them, as we did.

We retrospectively reviewed the use of PDT to treat AK in daily clinical practice. This approach is well tolerated, with a good rate of response that is long lasting. However, it is essential to take the site of the lesions into account when planning treatment. The results are excellent for the face, both in terms of response and tolerability. The scalp responds worse and is the site least able to tolerate treatment. The dorsum of the hands is the area with the poorest response, yet treatment was well tolerated. This seems to indicate that it would perhaps be more effective to apply a larger number of sessions or to repeat sessions for lesions

on the scalp and dorsum of the hands. At these sites, 3 sessions should be planned instead of 2, and these could be interrupted if a favorable response is obtained.

A review of the literature revealed that ours is the first retrospective study to analyze this technique with patients in daily clinical practice. It is also the first study to evaluate and prove the effectiveness of fluorescence diagnosis in predicting the response to treatment. Further studies with more patients are necessary to enable optimal use of PDT in the treatment of AK.

### Conflicts of Interest

The authors declare no conflicts of interest.

### References

1. Golman MP. *Terapia fotodinámica*. 1.<sup>a</sup> ed. Madrid: Editorial Elsevier; 2006.
2. Glogau RG. The risk of progression to invasive disease. *J Am Acad Dermatol*. 2000;42 Pt 2:23-4.
3. Gilaberte Y, Serra-Guillén C, de las Heras ME, Ruiz-Rodríguez R, Fernández-Lorente M, Benvenuto-Andrade C, et al. *Terapia fotodinámica en Dermatología*. *Actas Dermosifiliogr*. 2006;97:83-102.
4. Marquet A, Fernández-Guarino M, Pérez-García B, Harto A, Jaén P. *Terapia fotodinámica en dermatología*. *Dermatología Práctica*. 2006;14:30-5.
5. Smits T, Robles C, Van Erp PE, Van der Kerhof PC, Gerritsen MJ. Correlation between ppIX and fluorescence diagnosis in psoriasis and actinic keratoses using a digital fluorescence imaging system. *Book of Abstracts of the Annual Meeting of the European Society for Photodynamic Therapy*. Italy, Brescia; 2005. p. 57.
6. Olsen EA, Abernethy L, Kulp-Shorten C, Callen JP, Glazer SD, Huntley A, et al. A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. *J Am Acad Dermatol*. 1991;5:738-43.
7. Fernández-Guarino M, García-Morales I, Harto A, Montull C, Pérez-García B, Jaén P. *Terapia fotodinámica: nuevas indicaciones*. *Actas Dermosifiliogr*. 2007;98:377-95.
8. Tarstedt M, Rosdahl I, Berne B, Svanberg K, Wennberg AM. A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix®) in actinic keratosis on the face and scalp. *Acta Derm Venereol*. 2005;85:424-8.
9. Szeimies RM, Barrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, et al. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol*. 2002;47:258-62.
10. Pariser DM, Lowe NJ, Stewar DM, Jarratt MT, Lucky AW, Pariser RJ, et al. Photodynamic therapy with topical methyl aminolevulinate (Metvix®) is effective and safe in the treatment of actinic keratosis: results of a prospective randomized trial. *J Am Acad Dermatol*. 2003;48:227-32.
11. Morton C, Campbell S, Gupta G, Keohane S, Lear J, Zaki I, et al. Intraindividual right-left comparison of topical methyl-

- aminolevulinic acid-photodynamic therapy (MAL-PDT) and cryotherapy in subjects with actinic keratosis: a multicentre, randomized controlled study. *Br J Dermatol.* 2006;155: 1029-36.
12. Freeman M, Vinciullo C, Francis D, Spelman L, Nguyen R, Fergin P, et al. A comparison of photodynamic therapy using topical methyl aminolevulinic acid (Metvix<sup>®</sup>) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. *J Dermatol Treat.* 2003;14:99-106.
  13. Ericson MB, Sandberg C, Stenquist B, Gudmundson F, Karlsson M, Ros AM, et al. Photodynamic therapy for actinic keratosis at varying fluence rates: assessment of photobleaching, pain and primary clinical outcome. *Br J Dermatol.* 2004;151:1204-12.

## ERRATA

In the article entitled *“Selectivity of Photothermolysis in the Treatment of Port Wine Stains Using Multiple Pulses With a Pulsed Dye Laser”* and signed by I. Aldanondo, P. Boixeda, M. Fernández-Lorente, A. Marquet, M. Calvo, and P. Jaén (*Actas Dermosifiliogr.* 2008;99:546-54), the name of one of the authors of the article—Dr E. Martín-Sáez—was omitted.