NOVELTIES IN DERMATOLOGY

Daylight-Mediated Photodynamic Therapy in Spain: Advantages and Disadvantages

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Abstract Photodynamic therapy (PDT) is an option for the treatment of actinic keratosis, Bowen disease, and certain types of basal cell carcinoma. It is also used to treat various other types of skin condition, including inflammatory and infectious disorders. The main disadvantages of PDT are the time it takes to administer (both for the patient and for health professionals) and the pain associated with treatment. Daylight-mediated PDT has recently been reported to be an alternative to the conventional approach. Several studies have shown it to be similar in efficacy to and better tolerated than classic PDT for the treatment of mild to moderate actinic keratosis. Nevertheless, most of these studies are from northern Europe, and no data have been reported from southern Europe. The present article reviews the main studies published to date, presents the treatment protocol, and summarizes our experience with a group of treated patients.

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KEYWORDS
Photodynamic therapy; Daylight-mediated photodynamic therapy; Methylester of 5-aminolevulinic acid; 5-aminolevulinic acid; Actinic keratosis; Treatment

PALABRAS CLAVE
Terapia fotodinámica; Terapia fotodinámica con luz de día; Metiléster del ácido 5-aminolevulínico; Ácido 5-aminolevulínico;
Queratosis actínicas; Tratamiento
tolerada que la TFD clásica en el tratamiento de queratosis actínicas leves-moderadas. No obstante, la mayoría de los estudios realizados proceden del norte de Europa, y no existen por ahora resultados en países de la latitud de España. El presente artículo revisa los principales estudios publicados hasta el momento, expone el protocolo de utilización y resume nuestra experiencia en un grupo de pacientes tratados.

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Introduction

Photodynamic therapy (PDT) has become established as a treatment for actinic keratosis (AK), Bowen disease, and certain types of basal cell carcinoma over the past decade because it is highly effective for these dermatoses and gives excellent cosmetic results.1-5 PDT is currently included in clinical guidelines for treating nonmelanoma skin cancers;1,4,6-10 and is considered the first line of therapy for multiple AKs and field cancerization.4,11-15 The range of indications for PDT has broadened in recent years and now encompasses infectious conditions,16-19 inflammatory dermatoses,8,20-22 adnexal diseases,23-25 skin tumors,17,26-28 and photoaging.8,29-31 The potential value of PDT as a preventive treatment in transplant patients or those with conditions that are difficult to manage, such as Gorlin syndrome, has also been recognized.32-36 However, the application of conventional PDT10 is a laborious, time-consuming process for health professionals and patients alike and requires special equipment that takes up space in a clinic. The classic protocol10 specifies that the photosensitizer should be applied and kept covered (occlusion) for a certain period—usually 4 to 6 hours or more for 5-aminolevulinic acid (5-ALA) or 3 hours for the 5-ALA methyl ester, or methyl aminolevulinate (MAL). After incubation, the area is exposed to an appropriate source of light. The most common combinations of light sources and doses used in Europe are the Aktilite (Galdema, Lau sanne, Switzerland) at 37 J/cm² for approximately 8 minutes and the Waldmann PDT 1200L (Waldmann GmbH & Co, Villingen-Schwenningen, Germany) at 75 to 100 J/cm² for approximately 20 minutes. PDT is not free of adverse effects.37-44 The most common one, and the most limiting, is pain during illumination, which must sometimes be interrupted; analgesia or local or regional anesthesia may be required.45,46

With the use of portable light sources (Fig. 1) to optimize the procedure and facilitate outpatient treatment,47-49 the concept of ambulatory PDT has emerged.50 This modality is costly, however, and is only useful for treating small lesions. The most important methodological simplification introduced in recent years has been the therapeutic use of daylight.51,52

Daylight-Mediated PDT

Daylight PDT uses a combination of direct and reflected sunlight outdoors.53 Using the sun as a light source has encouraged more widespread use of PDT, has lowered costs considerably, and has enhanced adherence.

Clinical Trials and Other Published Studies

The available publications are summarized in Table 1. Strasswimmer and Grande54 suggested in 2006 that daylight could activate a photodynamic reaction, a claim that others disputed.55 Batchelor and colleagues56 were the first to report the effective use of daylight PDT to treat multiple scalp AKs in a 90-year-old patient who showed good tolerance of the session. The most important work on this modality has been published since 2008 by the group of Wiegell and colleagues at Hospital Bispebjerg in Denmark. Most of their studies have enrolled patients with AK (Table 1). In a pilot study with 29 patients they initially demonstrated that daylight-mediated PDT was as effective against AKs as red-light PDT using a light-emitting diode as the source; daylight therapy was also much less painful.52 The authors suggested that progressive, slower activation of protoporphyrin IX [PpIX] by small amounts of the photosensitizer (rather than rapid activation of large amounts of PpIX in the target tissue after several hours of incubation) might reduce the pain associated with treatment; they also suggested that since red and blue light fall within the spectrum of daylight, this source might be effective in therapy and also facilitate treatment. The use of natural light, therefore, could theoretically be useful and enhance therapy. In a later study they compared the efficacy of daylight-mediated PDT using MAL at concentrations of 16% and 8%, observing no differences in response rates, grades of erythema or pain between patients using the different concentrations.56 The authors suggested that MAL concentrations lower than the usual one of 16% could be effective. In 2011 they published the results of the first multicenter trial of daylight PDT in patients with nonhyperkeratotic AKs, finding that outcomes after exposures of 1.5 and 2.5 hours were similar.57 The authors recommended a 2-hour exposure time. The 2 later studies confirmed the earlier findings that daylight PDT is effective in nonhyperkeratotic AK. However, this modality proved less effective on hyperkeratotic AK lesions.58

Braathen59 reported similar results for daylight PDT used to treat facial and scalp AKs in a series of 18 patients in a private practice setting.

The results of a multicenter randomized controlled trial in Australia were recently presented by Shumack and colleagues at the Euro-PDT meeting (the annual conference of the European Society for Photodynamic Therapy in Dermatology) in Madrid from May 31 to June 1, 2013. This study showed that daylight PDT was not inferior to conventional PDT and that it was better tolerated and preferred by both patients and the investigators. This study confirmed the findings of earlier ones done in Nordic settings52,56-58 and was the first undertaken in a country with a climate that is...
<table>
<thead>
<tr>
<th></th>
<th>Wiegell et al. 52</th>
<th>Wiegell et al. 56</th>
<th>Wiegell et al. 57</th>
<th>Wiegell et al. 58</th>
<th>Braathen 59</th>
<th>Shumack et al. a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year of publication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Randomized, controlled, single blind</td>
<td>Randomized, double blind</td>
<td>Randomized, multicenter</td>
<td>Randomized, multicenter</td>
<td>Retrospective case series</td>
<td>Multicenter, randomized, blinded, within-patient controlled</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td>Denmark</td>
<td>Denmark</td>
<td>Denmark</td>
<td>Denmark</td>
<td>Switzerland</td>
<td></td>
</tr>
<tr>
<td><strong>No. of participating centers</strong></td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>To compare conventional red-light PDT to daylight PDT without occlusion</td>
<td>To compare response rates and adverse events in daylight PDT with 8% or 16% MAL</td>
<td>To compare the efficacy of daylight PDT with MAL after 1.5 or 2.5 h of exposure</td>
<td>To assess the efficacy of PDT with MAL in AK of different levels of severity.</td>
<td>To assess the feasibility of, adherence to, and satisfaction with daylight PDT in private practice</td>
<td>To assess the noninferiority of daylight PDT and the maximum pain caused</td>
</tr>
<tr>
<td><strong>Follow-up, mo</strong></td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>No. of treatment sessions</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>No. of cases</strong></td>
<td>29 (63–90)</td>
<td>30 (51–94)</td>
<td>120 (47–95)</td>
<td>145 (47–95)</td>
<td>18 (60–85)</td>
<td>100 (42–90)</td>
</tr>
<tr>
<td><strong>Age, y b</strong></td>
<td>73 (63–90)</td>
<td>71 (51–94)</td>
<td>72 (47–95)</td>
<td>72 (47–95)</td>
<td>72 (60–85)</td>
<td>66.9 (42–90)</td>
</tr>
<tr>
<td><strong>Sex, M/F</strong></td>
<td>23/6</td>
<td>26/4</td>
<td>96/24</td>
<td>117/28</td>
<td>12/6</td>
<td>75/35</td>
</tr>
<tr>
<td><strong>Grade of AK</strong></td>
<td>I, II</td>
<td>I, II, III</td>
<td>I</td>
<td>II, III</td>
<td>I, II</td>
<td>I, II</td>
</tr>
<tr>
<td><strong>Principal location</strong></td>
<td>Face, scalp</td>
<td>Face, scalp</td>
<td>Face, scalp</td>
<td>Face, scalp</td>
<td>Face, scalp</td>
<td>Face, scalp</td>
</tr>
<tr>
<td><strong>Surface area treated</strong></td>
<td>80 cm²</td>
<td>80 cm²</td>
<td>At least 25 cm²</td>
<td>At least 25 cm²</td>
<td>1-10 AKs</td>
<td>8 × 18 cm</td>
</tr>
<tr>
<td></td>
<td>Wiegell et al.⁵²</td>
<td>Wiegell et al.⁵⁶</td>
<td>Wiegell et al.⁵⁷</td>
<td>Wiegell et al.⁵⁸</td>
<td>Braaten⁵⁹</td>
<td>Shumack et al.ᵃ</td>
</tr>
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</tr>
<tr>
<td>Sunscreen</td>
<td>None</td>
<td>P20 (Riemann &amp; Co A/S, Hilleroed, Denmark)</td>
<td>P20</td>
<td>P20</td>
<td>Louis Widmer F15 gel</td>
<td>SPF 30</td>
</tr>
<tr>
<td>Time between application of sunscreen and photosensitizer</td>
<td>NA</td>
<td>15 min</td>
<td>15 min</td>
<td>15 min</td>
<td>5–15 min</td>
<td>NS</td>
</tr>
<tr>
<td>Photosensitizing agent</td>
<td>MAL 16%</td>
<td>MAL 16%, MAL 8%</td>
<td>MAL 16%</td>
<td>MAL16%</td>
<td>MAL 16%</td>
<td>MAL 16%</td>
</tr>
<tr>
<td>Amount of photosensitizer or layer thickness</td>
<td>1 g</td>
<td>1 g</td>
<td>‘‘Thick layer’’</td>
<td>1-mm layer</td>
<td>Layer of 0.5–1 mm</td>
<td>NS</td>
</tr>
<tr>
<td>Photosensitizer incubation</td>
<td>30 min on the daylight PDT side; 3 h on the conventional PDT side</td>
<td>Wait of 0–120 min before sun exposure</td>
<td>≤ 30 min</td>
<td>≤ 30 min</td>
<td>30 min</td>
<td>≤ 30 min</td>
</tr>
<tr>
<td>Occlusion after photosensitizer application</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Time of day for exposure</td>
<td>NS</td>
<td>11–18 h</td>
<td>8–18:30 h</td>
<td>NS</td>
<td>11–16 h</td>
<td>9–18 h</td>
</tr>
<tr>
<td>Exposure duration recommended</td>
<td>2.5 h</td>
<td>Rest of the day</td>
<td>1.5 h vs 2.5 h</td>
<td>1.5 h vs 2.5 h</td>
<td>90 min on a sunny day; 120 min on a partly cloudy or cloudy day</td>
<td>2 h</td>
</tr>
<tr>
<td>Light dose</td>
<td>Effective total exposure dose, 34.2 J/cm² (range, 11.7–65.9 J/cm²)</td>
<td>Mean effective dose, 30.1 J/cm² (range, 1.2–69.8 J/cm²)</td>
<td>Mean effective dose, 1.5 h, 8.6 J/cm²; in 2.5 h, 10.2 J/cm²</td>
<td>100 patients received &gt; 3.5 J/cm²; 37 patients received &lt; 3.5 J/cm²</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Weather conditions</td>
<td>Wiegell et al.\textsuperscript{52}</td>
<td>Wiegell et al.\textsuperscript{56}</td>
<td>Wiegell et al.\textsuperscript{57}</td>
<td>Wiegell et al.\textsuperscript{58}</td>
<td>Braathen\textsuperscript{59}</td>
<td>Shumack et al.\textsuperscript{a}</td>
</tr>
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</tr>
<tr>
<td>Sunny or partly cloudy</td>
<td>Sunny or partly cloudy</td>
<td>Sunny or partly cloudy</td>
<td>Sunny or partly cloudy; rainy or cloudy</td>
<td>&gt; 12°C, on days without rain</td>
<td>Sunny/partly cloudy</td>
<td></td>
</tr>
<tr>
<td>Results at 3 mo\textsuperscript{c}</td>
<td>3 patients exposed on cloudy or rainy days</td>
<td>Sunny or partly cloudy (83%); rainy or cloudy (17%)</td>
<td>Mean response rates: after 1.5 h, 77.2%; after 2.5 h, 74.6%</td>
<td>Mean response rates: 75.9% in AK I; 61.2% in AK II; 49.1% in AK III</td>
<td>Mean response rate, 77% (range, 0%-100%)</td>
<td>82% reduction in AKs</td>
</tr>
<tr>
<td>Pain (scale 0–10)</td>
<td>Mean maximum pain, 2 (1.9)</td>
<td>MAL 16%, 3.7 (2.4); MAL 8%, 3.6 (2.4)</td>
<td>0–1, 92%; 4–7, 7.5%; 8–10, 0.8%</td>
<td>NS</td>
<td>1 patient, 5 out of 10; others, 0</td>
<td>Mean, 0.8</td>
</tr>
<tr>
<td>Other adverse effects</td>
<td>Erythema, crusting</td>
<td>Erythema, crusting</td>
<td>Erythema, 74%; pustules, 29%</td>
<td>NS</td>
<td>Erythema, edema, crusting</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: ADV, Actas Dermo-sifiliográficas; AK, actinic keratosis; BJD, British Journal of Dermatology; F, female; M, male; MAL, methyl aminolevulinate; Mar, March; NA, not applicable; NS, not specified; Oct, October; PDT, photodynamic therapy; Sept, September.

\textsuperscript{a} Unpublished study, presented at the Thirteenth Conference of the European Society for Photodynamic Therapy in Dermatology (Euro-PDT) in Madrid, May 31 to June 1, 2013.

\textsuperscript{b} Age is shown as mean (range).

\textsuperscript{c} Response rate refers to the number of lesions showing complete response divided by the number of lesions treated in each patient.
very different from that of northern Europe. The same conference brought together reports of other smaller trials of daylight PDT. In one study, Grinblat and colleagues used 1 to 3 sessions to treat 14 patients with grade I or II AKs. The setting was Brazil and exposure was performed between 9 AM and 11:30 AM for a period of 60 to 90 minutes. Most patients experienced improvement. In the Netherlands, Venema used daylight-mediated PDT to treat 2 patients with actinic cheilitis, observing good clinical and cosmetic results. Tolerance was excellent. Le Pillouer-Prost presented the findings of a French study of 17 patients with grade I to III AKs. Five of the patients had been pretreated with fractionated carbon dioxide laser therapy. After 1 or 2 sessions of daylight PDT, depending on lesion thickness, most AKs in the pre-treated group had resolved. Lesions had also cleared in 10 of the 12 patients who had not been pretreated. Finally, Enk, described using this modality in 14 patients with nonulcerated cutaneous leishmaniasis in Israel. The patients were exposed to daylight in the hospital’s garden for 2.5 hours immediately after application of MAL. The cure rate was 86% after an average of 5 weekly sessions. Scarring was minimal and the procedure was painless.

The main conclusions of the most important studies and a discussion of the details of the different approaches to this form of PDT can be found in a Euro-PDT consensus paper.

Treatment Protocol

The only treatment protocol currently available for daylight-mediated PDT was proposed by Wiegell and colleagues and is summarized in Table 2. Considering that this PDT modality is at present off-label, the patient must be adequately informed about the procedure, its adverse effects, and efficacy. Written informed consent must be obtained. In order to assess the final outcome, baseline photographs of the area to be treated should be taken, and it may be useful to count and map the lesions in the field. Pretreatment with topical keratolytic agents may be advisable in some cases. Once the patient is in the treatment room, a sunscreen is applied to all exposed areas of the skin, even the area targeted for treatment. The sunscreen should provide a sun protection factor (SPF) of at least 20 and not contain physical, or inorganic, filters. Approximately 15 minutes after sunscreen application, the lesions should be scraped with a curette. A layer of MAL cream approximately 1 mm thick is then spread on the field to be treated. Occlusion is not needed. The patient should be outdoors and start exposing the area to daylight within half an hour of MAL application. The recommended duration of exposure is 2 hours, after which the remaining photosensitizer is removed and the skin is cleansed. The treated field should be protected from sunlight the rest of the day. Sun protection measures should be continued for at least the next 48 hours.

Key Questions and Concerns

What Patients Are Candidates for Daylight-Mediated PDT? This modality is mainly appropriate for cooperative patients who have multiple AKs (preferably grade I or II) or field can- cerization in sun-exposed areas and who find conventional PDT to be very painful. Daylight PDT will probably gradually come to be used for skin diseases other than AK.

What Light Dose Is Needed for Effective Activation of PpIX?

The amount of irradiation received in 2 hours of directed sunlight at midday varies greatly according to geographic location, weather conditions, and season. The threshold dose for PpIX activation (at which daylight PDT will be effective for destroying AKs) varies in studies published to date (8, 6, and 3.5 J/cm²). Until the effective dose is established more precisely, a threshold of 8 J/cm² is currently considered adequate to ensure that therapy will be effective. Using meteorological models and dosimeters installed at a number of geographic locations it has been possible to establish the effective light doses for activating PpIX in 2 hours of exposure at midday on the fifteenth day of each month at different latitudes. Accordingly, it would be possible to reach daylight doses over 8 J/cm² in Spain in any month, depending on weather conditions; this
Daylight-Mediated Photodynamic Therapy in Spain: Advantages and Disadvantages

Table 2  Protocol for Daylight-Mediated PDT. a

<table>
<thead>
<tr>
<th>Candidates for therapy</th>
<th>Patients with multiple AKs or field cancerization in sun-exposed areas.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment period</td>
<td>In Spain, all year long. 53</td>
</tr>
<tr>
<td></td>
<td>In Nordic countries, April to October. 57</td>
</tr>
<tr>
<td>Weather conditions</td>
<td>Avoid rainy 56 or very cloudy 51 days.</td>
</tr>
<tr>
<td>Procedure</td>
<td>Inside the hospital:</td>
</tr>
<tr>
<td></td>
<td>Apply a sunscreen (SPF ≥ 15 on exposed skin). 15 min</td>
</tr>
<tr>
<td></td>
<td>Scrape the lesions with a curette.</td>
</tr>
<tr>
<td></td>
<td>Apply a photosensitizer (MAL), without occlusion, on the field to be treated. 59</td>
</tr>
<tr>
<td></td>
<td>Outside the hospital:</td>
</tr>
<tr>
<td></td>
<td>Expose skin to natural light. 2 h</td>
</tr>
<tr>
<td></td>
<td>Remove remaining photosensitizer.</td>
</tr>
<tr>
<td></td>
<td>Strict sun protection measures for 48 h.</td>
</tr>
<tr>
<td>No. of sessions</td>
<td>AK, 1 session; for other lesions, variable no. of sessions.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Recommended: Examine the skin or contact the patient by telephone 24-48 h after treatment to check status; assess outcome 12 wk after treatment.</td>
</tr>
</tbody>
</table>

Abbreviations: AK, actinic keratosis; MAL, methyl aminolevulinate; PDT, photodynamic therapy; SPF, sun protection factor.

a Adapted from Wiegell et al. 57

b The ideal thickness remains to be established. The prescribing information recommends a layer 1 mm thick. However Wulf and colleagues have reported using a thinner layer without loss of efficacy (Dr. H. C. Wulf, personal communication at the thirteenth annual conference of the European Society for Photodynamic Therapy in Dermatology [Euro-PDT], in Madrid, May 31 to June 1, 2013).

How Should the Lesions Be Exposed to Daylight?
Exposure should take place outside in the middle of the day and last 2 hours. However, Grinblat and colleagues (unpublished, Euro-PDT meeting) used shorter exposure times of 60 to 90 minutes and observed results that were similar to those of multicenter studies. 57,58 Considering at the PpIX activation range corresponds to visible light, which passes through glass, Hospital Molhom in Vejle, Denmark, uses a glass structure to protect patients from certain weather conditions and increase comfort during exposure (Fig. 2).

What Period of the Year Is Most Appropriate for Daylight-Mediated PDT?
It seems to be possible to provide treatment at midday all year round in Spain unless there is a thick cloud cover. 53 Temperature may be a limiting factor, however, as studies in vitro and in mice suggest that low temperatures reduce PpIX production. 60-62 Low temperatures also make it difficult for the patient to stay outside during exposure. A temperature range of 10°C to 35°C for daylight PDT has been recommended, 63 but there is room for variation according to patient characteristics and exposure location. To date, no studies have demonstrated that there are differences in treatment efficacy outside this temperature range.

Wiegell and colleagues 64 a linear association between the UV index and the light dose that activates PpIX production during exposure at midday (11 AM to 1 PM) for 2 hours; when the UV index exceeds 3, patients receive over 8 J/cm² in this period. Weather conditions also play a part, as the effective daylight dose can decrease 25% on partly cloudy days, 50% on cloudy days, and 75% on rainy days. 53,65 The exposure time required on such days has not been determined, and although some authors recommend not scheduling this modality of PDT on rainy 66 or very overcast 63 days, it would be useful to more precisely determine the required conditions for delivering the minimum effective light dose.

Why Is a Sunscreen Needed and What Sunscreen Is Appropriate for PDT?
The recommendation to use a sunscreen aims mainly to prevent the adverse effects of UV radiation during exposure to sunlight. Sunscreens used to date have varied in their SPF levels, ranging from SPF 15 58 to SPF 20, 53,57 to SPF 30 and SPF 50 (by Grinblat and colleagues and by Le Pillouer-Prost, respectively; unpublished reports, Euro-PDT meeting). Similar outcomes have been observed with all of

Table 3  Light Dose Received in 2 h of Exposure at Midday in the Middle of Each Month at the Range of Latitudes in Which Spain Is Included. a

<table>
<thead>
<tr>
<th>Latitudes</th>
<th>Effective Light Dose in 2 h of Exposure on a Sunny Day, J/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Months</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>50 N</td>
<td>13</td>
</tr>
<tr>
<td>40 N</td>
<td>23</td>
</tr>
<tr>
<td>30 N</td>
<td>33</td>
</tr>
</tbody>
</table>

a Spain extends from about 30° N (Punta de Tarifa) to 43° 47’ N (Estaca de Bares). Columns show months by number. Months are expressed as numbers; 1 indicates January, 2 indicates February, etc. Adapted from Wiegell et al. 53

Table organization:
- Table 2: Protocol for Daylight-Mediated PDT
- Table 3: Light Dose Received in 2 h of Exposure at Midday in the Middle of Each Month at the Range of Latitudes in Which Spain Is Included
Figure 2  Greenhouse where the patient is exposed to daylight for photodynamic therapy at Hospital Molhom in Vejle, Denmark. Photograph kindly provided by Dr Peter Bjerring.

despite these sunscreens. It is important to use one that does not contain mineral filters, which might block the visible light necessary for PpIX activation in addition to UV radiation. A list of sunscreens appropriate for use in daylight-mediated PDT has been provided by the Spanish company Laboratorios Galderma SA. It includes the following products: from Laboratorios Uriage, Bariesun cream, SPF 30/50; from Laboratorios Ducray, Melascreen solar emulsion, SPF 50; from Laboratorios Eucerin, Sun Spray transparent, SPF 30/50; from Laboratorios Bioderma, AKN Mat SPF 30/UV-A 13, MAX cream, SPF 50+/UV-A 38 and AKN Spray SPF 30/UV-A13; and from Laboratorios ISDIN, a transparent SPF 30 gel-cream.

What Limitations Affect Daylight-Mediated PDT?
Daylight-mediated PDT is of great benefit for certain patients and for dermatologists who have neither the time nor the infrastructure for conventional PDT. However, there are certain limitations, such as the difficulty of scheduling sessions because of unpredictable weather and the constraints imposed by climate conditions in some geographic areas. At northern European latitudes, solar radiation is insufficient and temperatures are too low to accommodate sessions during some seasons (autumn and winter). Conditions in countries like Spain are different. It is still unclear whether very intense exposure for 2 hours at our latitudes might be risky for our patients, but the Australian clinical trial described above has shown that daylight-mediated PDT is effective and safe in countries with strong solar radiation. Another problematic issue is the lack of rigorous control

Figure 3  Results of treating multiple AKs with daylight photodynamic therapy (PDT). Photographs in the left column show lesions before treatment. Photographs on the right show the same lesions after treatment. Follow-up images in cases 1 to 3 (Complexo Hospitalario Universitario de Vigo, of the Integrated Management System in Vigo) were taken 3 mo after a single PDT session. Follow-up images in cases 4 and 5 (Hospital San Jorge, Huesca) were taken 8 mo after 1 PDT session and 4 mo after 2 PDT sessions, respectively.
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Figure 4  A, Baseline appearance of treated actinic keratosis lesions. B, Erythema and inflammation 3 h after treatment. The lesions in the upper photographs (1A and B) were treated with daylight photodynamic therapy (PDT). The lesions in the lower photographs (2A and B) were treated with conventional PDT. Photographs from Hospital San Jorge.

over therapy during the ambulatory outdoor period of the procedure, as the patient is the one who monitors illumination. To date, we still do not know the impact these possible differences might have on the effectiveness of therapy. In addition, daylight PDT seems to be less effective than conventional PDT for grade III AKs, and for the moment we lack sufficient evidence to support daylight-mediated PDT for other types of skin lesions. We expect to have new data in the future, however.

Our Hospital Departments’ Experience

The dermatology services under the Integrated Management System in Vigo [Complejo Hospitalario Universitario de Vigo (CHUVI)] and Hospital San Jorge in Huesca [HSJ] have used daylight-mediated PDT in 35 [CHUVI] and 9 [HSJ] patients with multiple grade I, II or III AKs, or field cancerization. Lesions were located on the face and/or scalp (CHUVI and HSJ) or legs (HSJ). Most patients were treated in a single session, but some underwent 2 sessions (HSJ). The results (Fig. 3) were similar to those achieved with conventional PDT for grade I or II AKs but inferior for grade III AKs. The main adverse effects were inflammation and crusting in the treated area. These effects were less intense, however, than those usually seen after conventional PDT (Fig. 4). Patients treated in the CHUVI reported less pain (scores, 0–3 on a scale of 0 to 10) after daylight mediated PDT than after conventional PDT (scores, 6–10) Most patients who had previously undergone conventional PDT expressed a clear preference for the daylight-mediated modality. The use of this approach allowed us to schedule treatment more quickly and accommodate all of them. Daylight was particularly useful for treating CHUVI patients who lived outside the city, and this choice also considerably reduced the amount of time the CHUVI staff spent preparing and supervising therapy.
Conclusions

Daylight-mediated PDT is an important new modality in dermatology. It has proven to be as effective as conventional PDT for treating AK and is a technically simpler method. Tolerance of therapy has improved considerably with the use of natural light. Both patients and specialists often express a preference for daylight PDT because the ambulatory procedure is simple and easy to organize. However, important disadvantages are that it is difficult to schedule because of weather conditions at certain times of the year and because light exposure is difficult to control. Over time, this modality will probably begin to have applications in the treatment of skin conditions other than AK, as has occurred with conventional PDT in recent years.

Although a protocol for daylight-mediated PDT has been proposed and an international consensus paper has been published, many aspects remain speculative to a certain degree and need to be defined in the short-term so treatment can be fully standardized. Some of these aspects are the obligatory use of a sunscreen, the most appropriate SPF for this clinical use, the ideal amount and concentration of photosensitizer, whether occlusion is necessary, the effective daylight dose required for PpIX activation, the exact exposure time required at different times of day and in specific weather conditions, the real effect of ambient temperature on efficacy, and the possible use of photosensitizers other than MAL.

According to information available at this time, Spain has an ideal climate for providing daylight PDT all year round. Existing international treatment protocols are currently based on conditions in Nordic countries. In order to adapt them to other settings, a clinical trial is currently under way in several European countries, including Spain, and the results are expected to be available soon. The findings will help us establish optimal procedures for applying daylight PDT in Spain.

Conflicts of Interest

Dr Lidia Pérez has attended Spanish and international meetings about PDT at the invitation of Laboratorios Galderma SA; she was a speaker at the first meeting organized by that company on PDT in Galicia. Dr Yolanda Gilaberte has received consulting fees from Laboratorios Galderma SA; she has received fees for speaking for that company at various conferences.

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References


15. Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 2: Emerging indications—field cancerization, photorejuvenation and
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