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CONTROVERSIES IN DERMATOLOGY

Studies of Methyl Aminolevulinate Photodynamic Therapy for Actinic Keratosis

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Abstract
Photodynamic therapy (PDT) for the treatment of actinic keratosis has been shown to be effective and safe in large clinical trials published in the last 5 years. However, evidence has since emerged that raises questions or that introduces new issues, such as the management of field cancerization, fluorescence diagnosis and results in transplant recipients. There also remains a need for more studies comparing PDT to additional treatments. We review the literature on these new topics in PDT.

PALABRAS CLAVE
Terapia fotodinámica;
Metilaminolevulinato

Terapia fotodinámica: estudios con metilaminolevulinato en queratosis actínicas

Resumen
La terapia fotodinámica (TFD) se ha mostrado eficaz y segura en el tratamiento de las queratosis actínicas (QA) en importantes estudios en los últimos 5 años. Sin embargo, desde entonces, se han publicado varios trabajos con alguna evidencia contradictoria o añadiendo nuevos aspectos de esta terapia para su discusión, como es el tratamiento del campo de cancerización, el diagnóstico de fluorescencia, los resultados en pacientes trasplantados o la ausencia de estudios comparativos con otros tratamientos. En este trabajo revisamos estos nuevos aspectos de la TFD.

Introduction

Photodynamic therapy (PDT) is indicated for the treatment of actinic keratosis, particularly when there are multiple lesions or severe damage from sun exposure, or when a patient with a fair-skin phototype is being treated. Several European countries, including Spain, approved PDT for this use in 2005. Several appropriately designed clinical trials with adequate sample sizes have looked at PDT alone or compared it to placebo or cryotherapy; their findings demonstrated response rates between 69% and 91% (Table 1), supporting the clinical application of this treatment in

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these early years.[1-5] More recent studies, however, have yielded inconsistent results or have looked more deeply into aspects of treatment that had not been previously considered and that are of particular interest for clinical management. Examples of issues that currently concern clinicians are field cancerization, response of lesions in different locations, cost-effectiveness, use in transplant recipients, and the development of new photosensitizing agents (Table 2).

Studies Comparing Methyl Aminolevulinate to δ-Aminolevulinic Acid in the Treatment of Actinic Keratosis

δ-aminolevulinic acid (ALA) and its ester methyl aminolevulinate (MAL) are the photosensitizing agents that are most often used in dermatology. Both are prodrugs that are metabolized to protoporphyrin IX by intracellular action of the enzyme ALA-synthase. ALA has been approved by the US Food and Drug Administration for treating actinic keratosis and superficial basal cell carcinoma with blue light. MAL was approved in Europe for the treatment of actinic keratosis and both superficial and nodular basal cell carcinoma. MAL is the more lipophilic agent, penetrating the target tissue more quickly, and therefore requires a shorter occlusion period, while systemic uptake is minimal.[6] A recent trial demonstrated that ALA (but not MAL) is absorbed by endothelial cells, explaining why ALA causes more dermal edema in treated lesions, and also why fractionated light therapy is only effective with ALA (not MAL).[7]

The literature we reviewed included a single study comparing the efficacy of these 2 photosensitizing agents.[8] That double-blind randomized trial compared the right and left areas of the scalps of 16 treated patients and found no statistically significant differences in effectiveness. Treatment with ALA was more painful than treatment with

Table 1 Facts About Photodynamic Therapy for Actinic Keratosis

Cure rates (69%-91%) are similar for PDT and cryotherapy in actinic keratosis
Cosmetic outcomes are better with PDT than with cryotherapy
Nonhypertrophic actinic keratosis appears to respond better to treatment with PDT
The best response rates for PDT are achieved when treating facial actinic keratoses
Two sessions give better results than a single session
The protocol applied most often is 2 sessions separated by 1 to 3 weeks
In principle, ALA patches are as efficacious as MAL
PDT is the most costly treatment, but its cost-effectiveness is in line with that of cryotherapy
Patients prefer PDT

Abbreviations: ALA, d-aminolevulinic acid; MAL, methyl aminolevulinate; PDT, photodynamic therapy.

Table 2 Controversies in Photodynamic Therapy for Actinic Keratosis

Trials comparing PDT to forms of treatment other than cryotherapy (eg, imiquimod, 5-fluorouracil, diclofenac) are lacking
All light sources used to date have been effective, although comparative trials are lacking
Less concentrated MAL doses have been equally effective
Occlusion times less than 3 hours have been reported to be effective
The role of fluorescence diagnosis is still uncertain
The treatment of field cancerization still needs to be studied specifically and PDT in this setting needs to be compared to other treatment approaches
Comparative, long-term studies in transplant recipients are lacking

Abbreviations: MAL, methyl aminolevulinate; PDT, photodynamic therapy.

Table 3 Differences between δ-Aminolevulinic Acid (ALA) and Methyl Aminolevulinate (MAL)*

ALA	MAL
FDA approved for the treatment of actinic keratosis and basal cell carcinoma	Approved in Europe for the treatment of actinic keratosis and superficial and nodular basal cell carcinoma
Incubation: 14–18 h	Occlusion: 3 h
Blue-light illumination, 10 J/cm^2 for 16 min (BLU-U®)	Red-light illumination, 37 J/cm^2 for 8 min at a distance of 5-8 cm (Aktilite)
Unresolved lesions: re-treat after 8 wk	Unresolved lesions: re-treat after 7 d

*No significant differences between the 2 photosensitizing agents have been demonstrated.
Abbreviation: FDA, Food and Drug Administration.

MAL, however. A trial in which pain in the treatment of actinic keratosis with these photosensitizing agents was assessed found that 14% of MAL-treated patients abandoned application (vs 54% of those treated with ALA).[9] Table 3 summarizes the differences between ALA and MAL.[10,11]

ALA patches for PDT have recently been developed and will soon be launched on the Spanish market. The development of these patches included properly designed phase III trials under the direction of a group of experts led by Szeimies.[12,13] The effectiveness of these patches has been found to be similar to MAL, with cure rates of 86% to 89% in actinic keratosis, and to be significantly superior to cryotherapy when a single treatment session is given (P=.007). The results of single-session treatment are maintained 12 months later, as demonstrated by a finding of larger percentages of responsive lesions that were still clear after use of ALA patches in comparison with placebo patches or cryotherapy.[14]

An innovative system has been used to manufacture these new hydrocolloid patches, which facilitate occlusion of up to 4 cm.[2] Each patch contains 8 mg of ALA and covers the surface for 4 hours with no need for curettage.

A priori, the results of patch treatment do not seem to be inferior in well-designed studies, but there remain questions such as how to use patches to treat field cancerization (several adjacent patches would have to be applied) and how to use them in fluorescence diagnosis.

Studies of MAL in PDT Using Different Light Sources to Treat Actinic Keratosis

Various light sources, emitting both laser and noncoherent light, have been used in PDT. All emit light at about 600 nm in the last Q band of the porphyrin spectrum and penetration is adequate for treating actinic keratosis. The most commonly used is a pulsed dye laser, which can operate at 595 nm, minimizing side effects such as purpura, hyper- or hypopigmentation, or scarring. A wide variety of noncoherent light sources have proven useful. Among them are broadband light, light-emitting diodes (LED), intense and variable pulsed light, sunlight, and even portable devices for home use. All have been shown to be effective and no study has yet found one to provide better results than another.

Two studies have investigated pulsed dye laser and MAL treatment of actinic keratosis. In the first, published in 2006, Alexiades-Armenakas[15] reported satisfactory treatment of various skin diseases (actinic keratosis, basal cell carcinoma, and acne) with pulsed dye laser (595 nm) and MAL, but the author did not include concrete data in the article. The second publication, comparing 595-nm pulsed dye laser to broadband light with MAL for treating patients with basal cell carcinoma or actinic keratosis, found no differences in results obtained with the different light sources.[16]

Recent studies have looked at LED devices, which were introduced after the broadband light sources used initially. Some authors claim that LED sources are superior as they are safer, emit less heat, work at a lower voltage, and require shorter therapeutic exposure times. Additionally, penetration is greater, as light is emitted within a narrower band, with improved photodynamic response. Nevertheless, no studies have demonstrated superior outcomes for LED devices in comparison with broadband light sources. What has been shown to date is that outcomes are similar, given that differences in cure rates have been nonsignificant.[27-19]

Intense and variable pulsed light sources for PDT have also been studied. The variable source gives a type of intense pulsed light but allows the number of pulses, wavelength, and the intervals and distances between pulses to be modified. Both have proven effective in PDT and able to work in combination to prevent photoaging. The variable source has also been found to cause less pain than LED treatment.[20,21]

Sunlight has likewise been useful and effective in the interesting trials of Wiegell and colleagues,[22,23] who used dosimeters to determine the sunlight doses received during treatment lasting up to 6 hours after occlusion of an area with MAL. There were no statistically significant differences between sunlight and LED treatment (clearing of 79% of lesions with sunlight and 71% with LED illumination), although natural light was found to be significantly less painful.

Finally, the British group of Moseley and colleages[24,25] has studied portable PDT devices for home use after occlusion with photosensitizing agents. These devices also proved effective. Table 4 summarizes the attributes of PDT light sources, including doses and outcomes.

We can conclude that light source is not an issue in PDT, as many devices have been shown to be effective. No light source has proven ideal for all indications. The choice of one over another will depend on factors such as availability, cost, time, location of lesions, or the process being treated. However, as we clearly lack studies comparing different light sources, more work is needed.

Location of Lesions and Special Characteristics

In the earliest studies of PDT, the most intensely keratotic lesions were less responsive to treatment; they therefore required pretreatment with curettage or keratolytic agents and more sessions[4] due to lower penetration by the photosensitizing agents and light.[10] Later studies have produced inconsistent results in this regard. The important group of Szeimies and colleagues[14] reported similar results in 2009 for the treatment of thin and thick lesions with MAL; they explained their results by noting that they had used red LED illumination rather than the broadband light used in most studies. Can the use of different light sources truly explain the similar outcomes in thick and thin lesions, however? Wavelength, which determines tissue penetration, is the same for both types of light, although LEDs emit within a narrower band. More controversial is the study of Brathen and colleagues,[26] who saw better outcomes in thick lesions than thin ones after an incubation period of 1 hour. They studied only 4 cases and did not use any statistical tests for their comparison. Nor was the incubation time sufficient for treatment of actinic keratosis. Their findings, therefore, appear to be anecdotal.

Table 4 Light Sources Used in the Photodynamic Treatment of Actinic Keratosis

Light Source	Wavelength	Dosing	Example	Advantages	Disadvantages	Outcomes
PDL	595 nm	9-12 J/cm^2, 6 ms at 9 mm, 50% overlap	Vbeam (Candela®)	High intensity	Harder to manage than noncoherent light sources	Expert opinion
				Short treatment time	Higher cost	Effectiveness similar to LED in 1 study
				Lesion selectivity		
Broadband	580-720 nm	75 J/cm^2	PDT 1200 (Waldmann®)	Several wavelengths; various PAs can be used	Considerable heating	Many studies report effectiveness. Not inferior to LED or PDL
LED	630 nm	37 J/cm^2	Aktilite® (Photocure)	No heating	Cannot be used for extensive areas (scalp)	Several studies: not inferior to other light sources
				Less time		
				Deeper penetration		
IPL/VPL	550-590 nm	24 J/cm^2	Lumenis one®	Less painful	Few RCTs	Single RCT: VPL not inferior to LED
				Various wavelengths		
				Treatment of photoaging		
Sunlight	Full visible spectrum	Calculated by dosimeter (effective red light)	NA	Cheap, simple, ambulatory treatment	Difficult to control dose	Several studies: not inferior to LED
				Well tolerated		
Portable device	550-750 nm	45-60 J/cm^2	OLED (Osram Opto semiconductors®)	Cheap, simple, outpatient treatment	Only for isolated lesions (diameter, 2 cm)	100% of lesions cleared
				Well tolerated	Patient-dependent	No trial comparisons

Abbreviations: IPL, intense pulsed light; LED, light emitting diode; NA, not applicable; PA, photosensitizing agents; PDL, pulsed dye laser; RCT, randomized controlled trial; VPL, variable pulsed light.

With respect to lesion location, several studies have found that response is better for facial lesions than for those located on the scalp; some groups only provide descriptive analysis[2,5,27] but one reported statistically significant differences on comparison.[28] Such findings are usually explained by the fact that facial lesions are generally thinner than scalp lesions, and so photosensitizing agents and light penetrate more easily. This would also explain why response is poorer for lesions on the dorsal side of the hand than for facial lesions.[13]

Comparison With Other Methods of Treatment

Later studies have found that cure rates are similar for treatment in 2 PDT sessions separated by 1 to 4 weeks and for cryotherapy.[1,2,4] However, there are still few trials comparing PDT to other treatments for multiple actinic keratoses or field cancerization. One trial comparing 5-fluorouracil to a single session of PDT with ALA showed that the light therapy was as effective as 3 weeks of treatment with 5-fluorouracil and that the cosmetic result was considered better after PDT.[29] No trials comparing PDT and imiquimod or topical diclofenac have been published. Cure rates of 54% of lesions have been reported for 8 weeks of treatment with imiquimod applied 3 times per week, the regimen usually followed in Europe; this implies that the effectiveness of imiquimod is superior to that of PDT. The findings for imiquimod treatment applied 3 times per week for 16 weeks, the regimen used to treat actinic keratosis in the United States, were similar: a cure rate of 84% has been reported.[30]

The guidelines of the British Association of Dermatologists include PDT among the treatment options for actinic keratosis, with a grade B level of recommendation and an evidence level of 1. Both cryotherapy and 5-fluorouracil have a higher level of recommendation (A) supported by level-1 evidence.[31] However, the clinical practice guidelines of the European Dermatology Forum give PDT, 5-fluorouracil, and cryotherapy the same classification

Table 5 Summary of Recommendations in Guidelines for the Treatment of Actinic Keratosis, from the British Association of Dermatologists[31] and the European Dermatology Forum[32]

	Cryotherapy	5-Fluorouracil	Imiquimod	PDT
Level of evidence	IA-IIB	IA- IIC	IB-IIB	IB- IIB
Number of lesions				
Few	Good treatment	Good treatment	May be used, depending on circumstances	Use exceptionally
Many	Appropriate treatment	Good treatment	Appropriate treatment	Good treatment
Lesion thickness				
Thin	Appropriate treatment	Good treatment	Appropriate treatment	May be used, depending on circumstances
Thick	May be used, depending on circumstances	Use exceptionally	Use exceptionally	Use exceptionally
Recalcitrant	Appropriate treatment	Appropriate treatment	Appropriate treatment	Appropriate treatment

Abbreviation: PDT, photodynamic therapy.

of II-B and no other treatment method is presented as superior.[32] The recommendations for actinic keratosis from both sets of guidelines are summarized in Table 5. In conclusion, we might say that PDT offers advantages over other treatment modalities when multiple lesions are present; in areas where actinic damage is more intense; or if lesions are located on the face, where response is good, recurrence occurs, and the cosmetic outcome is important.

In the various studies that have compared patients' preferences, the high scores given to light therapy in comparison with other modalities has been noteworthy. A 2006 study by Morton and colleagues[5] compared PDT, cryotherapy, topical 5-fluorouracil, topical diclofenac, and surgical excision. Patients favored PDT (although it was not more efficacious in the study) and found it to be more cosmetically satisfying. In 2008, Tierney and colleagues[33] compared PDT, imiquimod, and surgery for the treatment of actinic keratosis in 45 patients. Patient opinions were recorded on several aspects: recovery time, cosmetic outcome, cost, effectiveness, and overall preference. PDT was significantly superior in all aspects according to patient' opinions. Two other studies also found that patients favor PDT over other approaches.[4,9] To date, therefore, the literature does not allow us to affirm that PDT is the superior treatment for actinic keratosis, but we can see that patients do prefer light therapy.

Pain Treatment

Pain during irradiation from the PDT light source is without doubt the main limitation of this modality. Between 60% and 80% of patients experience slight to moderate pain,[34] and the discomfort has even become intolerable for 54%.[9] Patients have found PDT to be as painful as cryotherapy[5] and less painful than application of 5-fluorouracil.[35]

Local measures to alleviate pain, such as the use of fans or applying water, are generally adequate for helping the patient to tolerate the session; both measures have been shown to significantly diminish pain.[36] Topical anesthetics are inappropriate, as the pH of these agents interferes with the activity of topical MAL. Local injection of a vasoconstrictor is also inappropriate, as it reduces blood flow and oxygenation, which are essential for the oxidative reaction in PDT. In the future, pain treatment may involve nerve blocks, which are particularly indicated for patients with multiple actinic keratoses or intense actinic damage, as they are the ones who experience the greatest pain. A recent study published by dermatologists at the Oncology Institute of Valencia showed that supraorbital and supratrochlear nerve blocks safely and effectively controlled pain during PDT, and that these procedures were well tolerated by patients.[37] Furthermore, the blocks were significantly more effective than the application of cold air to irradiated zones during PDT in that study. Haldin and colleagues[38] also reported the effectiveness of nerve blocks in this setting in 2009. They treated 10 patients, finding that nerve blocks were significantly better at alleviating pain than the absence of any pain control measure.

Special Considerations in the Use of PDT

Transplant Recipients

PDT has been effective in the treatment of actinic keratosis in patients who have received organ transplants. The first study in this setting was published in 2004 by Dagrieva and colleagues,[39] who found that active treatment was significantly superior 16 weeks after PDT (P=.0003). In 2007, a study in kidney transplant patients reported that

71% of lesions cleared, although the rate was only 41% for lesions located on the extremities.[40] A single trial has compared PDT to another therapy (5-fluorouracil) in transplant recipients. PDT achieved cure rates of up to 100% of lesions in that study and proved significantly better than treatment with 5-fluorouracil (P=.002).

However, to date, studies of the ability of PDT to prevent the development of squamous cell carcinoma over actinic keratosis have been inconclusive. The first study, published in 2004, was appropriately designed but found that PDT was not effective in this respect.[41] The second study, also properly designed and with a large sample (889 lesions in 81 patients) did find that fewer new actinic keratoses developed in treated patients but that the difference was not significant (P=.06).[42] Further study is needed to determine whether PDT can play a preventive role in this setting.

Field Cancerization

The term *field cancerization* was coined in 1953 by Slaughter, who applied it to all epithelial surfaces, including the skin, stating that "cancer does not arise as an isolated cellular phenomenon, but rather as an anaplastic tendency involving many cells at once."[43] Actinic keratosis is a field disease that is not confined to the lesions themselves. Mutations in p53 and mitochondrial DNA have been described up to 7 cm around squamous cell carcinoma patches or nodules. The risk of progression from actinic keratosis to squamous cell carcinoma is between 1.5% and 15%.[44] It is in the treatment of field cancerization that PDT offers its greatest advantages over cryotherapy, which is usually the standard therapy used for comparison. To date, however, no trial has compared PDT in this setting to any other approach, such as application of imiquimod, 5-fluorouracil, or diclofenac. Most studies published have looked at objective measures of actinic keratosis, counting lesions one by one and comparing results to cryotherapy. But if this were actually what we did in practice, it would be much better to treat patients with cryotherapy by this measure. In fact what we do in routine dermatology practice is treat areas with actinic damage, not isolated lesions. Why, then, do studies continue to analyze lesion by lesion if this is not how treatment is normally approached? PDT has already been shown to be as efficacious as cryotherapy for treating isolated lesions. One recent study even found that PDT is superior for lesions on the legs.[27] The time has come to study PDT for treating field cancerization. In 2008, Babilas and colleagues[18] became the first to publish on this application and since then only 1 additional study has appeared.[13] If we do not treat field cancerization with PDT, we will be unable to assess one of the main advantages of this approach. Both the aforementioned studies lack long-term follow-up comparisons to controls that would verify whether the PDT-treated field has a lower risk of developing new actinic keratoses or squamous cell carcinoma than untreated areas.

Another issue in the management of field cancerization is the possibility of combining various treatments at different moments when following a patient. In 2009, Safelburg[45] reported treating sequential patients with PDT followed by treatment with imiquimod. This regimen was well tolerated and cure rates of 90% were obtained with the 2 treatments in comparison with PDT alone (P=.023).

The treatment of field cancerization is the future of actinic keratosis management, yet we still lack studies on the use and long-term results of PDT in comparison with other field treatments.

Photodiagnosis

Photodiagnosis consists of quantifying and studying the red fluorescence of inflammatory, preneoplastic, and neoplastic tissues under illumination with Wood's light after a photosensitizing agent has been applied. Red fluorescence is due to the accumulation of protoporphyrin IX and has been linked to the development of cell damage, meaning that areas where fluorescence reveals levels of protoporphyrin IX to be high will be susceptible to such damage. Topical MAL has been shown to be the ideal photosensitizing agent for fluorescence diagnosis because it is more lipophilic, crosses cell membranes, is absorbed more quickly, and defines the lesions more clearly.

Various studies have put forth hypotheses that link fluorescence to treatment response. In 2004, Erickson and colleagues[46] reported using intensity of fluorescence in computer-processed images to monitor photobleaching of actinic keratoses or basal cell carcinoma lesions treated with PDT at different fluence rates, studying the correlation between fluence rate and outcomes. They concluded that photobleaching was correlated with results and was superior at lower fluence rates (30 mW/cm^2).

In 2008, Wiegell and colleagues[22] published an interesting study using computer measurement of fluorescence in photographic pixels in order to compare the effects of LED therapy and sunlight after occlusion with MAL for 3 hours. They found that fluorescence was much greater after LED exposure but that fluorescence in these patients decreased and the between-group differences had equalized from 3 to 5 hours later. Their conclusion was that daylight is as effective as LED therapy and is significantly less painful. A later study by the same group measured fluorescence once again in patients treated with sunlight (effective dose, 30 J/cm^2) and MAL at 2 concentrations (8% and 16%).[23] They found no differences in fluorescence or response between the 2 treatment groups. We can conclude that fluorescence is a labile parameter that is difficult to interpret and must be studied further before we can understand its meaning. It does not change with MAL concentrations but is dependent on time, light source, and epidermal characteristics.

After noting the lability of fluorescence, our group attempted to look more closely at the possibilities of fluorescence diagnosis by correlating fluorescence with response in treated areas. That study, published in this journal,[28] analyzed digital fluorescence images taken before and after treatment; we demonstrated a correlation with treatment response at 3 weeks. An important limitation, however, was the absence of computerized assessment of the areas. Without doubt, the role of fluorescence diagnosis is uncertain at this time. Fluorescence quantification is clearly not an objective at present and we lack software designed specifically for its analysis. Further

study is required to clarify the potential of this promising technique.

Cost of Treatment

PDT is the most expensive treatment if we look at it in isolation,[47] particularly in comparison with cryotherapy, which is used much more widely in routine practice. PDT, however, is equally cost-effective at 1 year. A study published in 2006 evaluated the cost of treating patients with multiple actinic keratoses with PDT and cryotherapy over 1 year, finding that outcomes were not significantly different and PDT was more expensive by only a pound.[48] PDT therefore is not as expensive as it might seem to be at first, particularly for medium- and long-term treatment of patients with multiple lesions corresponding to intense actinic damage. Another study, published in 2009, also supported this conclusion, finding that initial PDT treatment followed by other second-line treatments was the best combination for achieving complete response (91%) and that always using PDT increases the likelihood of excellent cosmetic results (73%).[49] In both studies, PDT was a cost-effective choice, equivalent to other treatment approaches.

Conclusions

The early years of PDT development and the application of this treatment modality in dermatology have seen great advances, but issues have come under debate and new aspects have been targeted for investigation. It seems clear that PDT is an approach that patients prefer and that cure rates are similar to cryotherapy in actinic keratosis. The cosmetic results are excellent and treatment is cost-effective, but we still need to know more about its use in field cancerization and transplant recipients. We also need to see more comparisons with other treatments and study fluorescence diagnosis. PDT is in the early phase of its application and dermatologists need to continue to study the technique in order to perfect it and understand it better.

Conflict of Interest

The authors declare no conflicts of interest.

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