Dermatologic Applications of Photodynamic Therapy: The University of Miami Outlook

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Photodynamic therapy with aminolevulinic acid followed by illumination with a variety of light sources provides broad therapeutic results for various dermatologic conditions. We undertook to review photodynamic therapy as it is practiced at the University of Miami, Florida, and its utility in treating cosmetically sensitive skin conditions, such as actinic keratoses, actinic cheilitis, photodamage, acne vulgaris, hidradenitis suppurativa, and verruca vulgaris.

The fundamental goal of the cosmetic dermatologist is to improve the appearance of an individual's skin, be it solely for aesthetic reasons or as part of treating underlying cutaneous conditions. The use of photodynamic therapy (PDT) in dermatologic practices is steadily growing and is becoming a fundamental therapy for a variety of skin disorders. Currently, the dermatologic application of PDT cleared by the US Food and Drug Administration (FDA) and available in the United States is 20% 5-aminolevulinic acid (ALA) for the treatment of nonhyperkeratotic actinic keratoses (AKs) on the face and scalp, using a blue light source and a drug incubation time of 14 to 18 hours.[1] However, off-label dermatologic applications of PDT are vast and include preneoplastic and neoplastic conditions (eg, actinic cheilitis [AC], disseminated actinic porokeratosis, basal cell carcinoma, squamous cell carcinoma, and cutaneous T-cell lymphoma), inflammatory disorders (eg, acne vulgaris, rosacea, hidradenitis suppurativa [HS], psoriasis, lichen planus and lichen sclerosus, scleroderma, and alopecia areata), infectious diseases (ie, verruca vulgaris [VV], molluscum contagiosum, tinea versicolor, and leishmaniasis), and chemopreventive indications for immunosuppressed patients.[2,3]

Presently, at the University of Miami, Florida, we use PDT for the approved indication of AKs as well as for the off-label indications of AC, photoaging, recalcitrant VV, acne vulgaris, and HS. In this article, we will draw upon our clinical perspective at the University of Miami to review the concept and role of PDT in dermatology along with its usefulness and mechanisms of action in the treatment of various skin conditions (Table).

The idea of selectively destroying targets using photosensitizers with light dates back to the early 1900s.[4] Yet, PDT was not integrated into the practice of dermatology until the 1990s, when topical photosensitizers were first introduced.[5] PDT works through a process of selective photocytotoxicity by which the specific target of destruction depends on the condition being treated. Initially, a topical or systemic photosensitizer is introduced and accumulates in the targeted sites (Figure 1).[6] Then, various light sources that have emission spectrums that correlate with the absorption spectrum of the photosensitizer are used to irradiate and, in effect, activate different cytotoxic mechanisms (ie, reactive oxygen species) in addition to various and yet-to-be-clarified immune effects.[6] Consequently, this phototoxic reaction leads to the apoptosis and necrosis of the targeted cells, with minimal influence on the surrounding tissue.

In general, the topical prephotosensitizers used by dermatologists are ALA in the United States and methyl ester of

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Protocols for Treatment With Aminolevulinic Acid and Photodynamic Therapy at the University of Miami, Florida

Indication	Pretreatment and Preparation	Incubation Time	Light Source	Follow-up	Average Treatments, No.
Actinic keratoses	Destruction of hyperkeratotic lesions (LN_2) Acetone or alcohol scrub	1–6 h	Blue LED	4–6 wk	2
Actinic cheilitis	Prophylaxis for HSV	30 min–1 h	Blue LED	4–6 wk	1
Photoaging	Destruction of hyperkeratotic lesions (LN_2)	30–60 min	IPL	4 wk	Varies
Acne vulgaris	Acetone scrub preparation, except for those with xerosis	30–60 min	Blue or red LED	2 wk with PDT followed by twice weekly with blue light alone for 4 wk	2 with PDT followed by 8 without PDT
Hidradenitis suppurativa	Acetone or alcohol	30–60 min	Blue or red LED	2 PDT treatments 3 wk apart followed by twice weekly without PDT	2 with PDT followed by 8 without PDT. Repeat as needed
Verruca vulgaris	Keratolytics (salicylic acid) Preparation by paring lesion	1–3 h	Long PDL (595 nm)	3–4 wk	Varies

Abbreviations: HSV, herpes simplex virus; IPL, intense pulsed light; LED, light-emitting diode; LN_2, liquid nitrogen; PDL, pulsed dye laser; PDT, photodynamic therapy.

ALA (MAL) in Europe. These prodrugs are metabolized by the skin to the photosensitizer protoporphyrin IX (PpIX). The increased penetration of the prodrug and the increased accumulation of PpIX result in the targeting of certain cells for destruction.[6] The use of other treatment methods, such as pretreatment curettage, paring, surface skin stripping, microdermabrasion, and acid peels, as well as retinoid, acetone, and alcohol application, can enhance the efficacy of the photosensitizers by augmenting their penetration through the stratum corneum.[6,7] The degree of penetration is additionally determined by the incubation time, the photosensitizer applied (ie, MAL penetrates more deeply than ALA), the individual patient, the site of application, and the skin condition being treated.[6] The depth of the PDT effect largely depends on the light sources used, such that illuminating instruments with longer wavelengths (ie, pulsed dye laser [PDL], intense pulsed light [IPL], and red light) have deeper permeation and activity than shorter-wavelength sources (eg, blue light).[3] Meanwhile, the highest absorption spectrum of PpIX corresponds to the Soret band (405 nm), which is the wavelength of blue light.

There are numerous PDT treatment protocols that have been reported and are currently used by dermatologists for various cutaneous conditions; over time, treatment methods should become standardized. To generate optimal management guidelines for PDT in dermatology, it is essential to share the diverse dermatologic applications of PDT as well as to continue appropriate investigative studies of this treatment.

Overall, dermatologic application of PDT is considered safe, effective, tolerable, user friendly, and cost effective.[7]

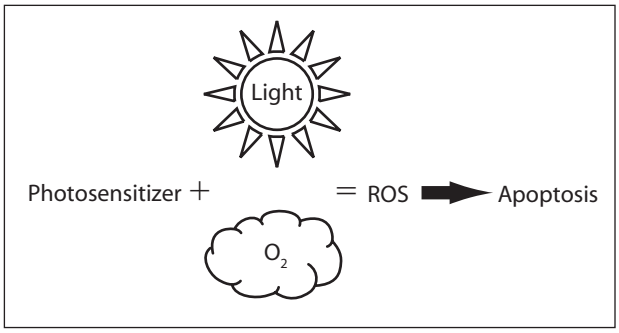

Figure 1. Schema of photodynamic therapy. ROS indicates reactive oxygen species.

The most appealing rationale for using PDT to treat a range of dermatologic diseases is the excellent and lasting cosmetic outcome associated with it and its noninvasiveness.[6,7] However, as with any destructive procedure, PDT is associated with some adverse effects, which result in a limited downtime of approximately 1 week. The most common adverse effects associated with PDT are minimal and temporary and include pain (eg, burning, itching, and stinging) during and shortly after the procedure, erythema, scaling, edema, crusting, eczematoid reactions, recurrence of herpetic infections, and postinflammatory pigmentation alterations.[7,8] The long-term risks of scarring, secondary infection, and severe allergic or phototoxic reactions are very rare.[7]

At the University of Miami, there are several steps that we perform before, during, and after PDT for all indications to minimize adverse effects and optimize the therapeutic result. Initially, each patient undergoes a consultation with a dermatologist to ensure qualification for PDT (ie, to rule out contraindications such as photosensitivity, pregnancy, Fitzpatrick skin type VI, and inability to comply with posttreatment instructions), realistic expectations and awareness of the risks and benefits of treatment, and pertinent off-label utility. After informed consent is given, pretreatment photographs are taken. Patients with histories of herpetic infections in the treatment area are prophylactically treated with antiviral therapy (ie, valcyclovir 1g twice daily for 3 days starting on the day before the procedure). Patients are also told to expect a downtime of up to 1 week and to avoid UV light for at least 48 hours posttreatment, after which any residual PpIX is converted to light-inactive hemes.

With the new, shorter incubation times now used with PDT, pain is seldom intense enough to cause discontinuation of therapy.[9] If patients complain of discomfort, the light source is pulled back slightly from the target area, effectively decreasing the activation dosage. For posttreatment discomfort, ice packs, cool-mist sprays, and analgesics (eg, ibuprofen or acetaminophen) can be employed. Photographs are taken immediately after the treatment session and at follow-up visits. Before patients leave the clinic, we make certain that they apply an appropriate sunscreen (eg, zinc oxide with a minimum sun protection factor of 30). We also reinforce the importance of strict adherence to the 48-hour sun-avoidance rule, which is critical in sunny regions like Miami, to prevent phototoxic consequences. In addition, we recommend nightly use of a topical moisturizer. In cases of severe photodamage, where activation is more intense, we prescribe twice-daily, midpotency, cream-based topical steroids for 3 days. We reserve the use of antibiotics for secondary infections and use of oral steroids for severe phototoxic or hypersensitivity reactions.

AKs AND AC

AKs and AC are common precancerous lesions that are classified on a developmental spectrum and have the potential to transform into squamous cell carcinoma, with AC having a higher predisposition for invasion.[10] AKs and AC usually manifest as multiple, pink-to-red, scaly papules on sun-exposed skin. Many treatment modalities (eg, cryotherapy, fluorouracil, imiquimod, and retinoids) have been designated to treat AKs for the purpose of preventing malignant progression. Recently, a number of clinical investigations have demonstrated the safety and efficacy of ALA/MAL-PDT as well as its superior cosmetic elegance in the treatment of AKs and AC.[10] Depending on the photosensitizer used, the number of treatments given, the area treated, the type of illuminator used, and whether pretreatment exfoliation is applied, complete response rates vary from 69% to 91%.[10] PDT has also been shown to be effective in the treatment of extensive AKs in immunosuppressed (ie, transplantation) patients, who have a particular predisposition for developing precancerous and cancerous cutaneous lesions.[3]

The mechanism of action of PDT for AKs and AC is straightforward: the accumulation of PpIX is up to 10 times higher in atypical skin epidermal cells than in normal cells, which translates into the selective targeting and destruction of the keratinocytic intraepidermal premalignant neoplasms characteristic of AKs and AC.[10-11] Extensive clinical investigations have revealed that a contact time shorter than that approved by the FDA (60 minutes vs 14–18 hours) for ALA-PDT in treating AKs provides the same efficacy but less inconvenience and fewer potential adverse effects.[12]

Our treatment protocol for AKs and AC begins with the pretreatment of hyperkeratotic AKs using various destructive methods (eg, liquid nitrogen, electrocautery). On the day that PDT is initiated, the patient is asked to wash the area of skin that is to be treated with a gentle cleanser and water. In sebaceous areas such as the face, the skin is wiped clean with acetone. In nonsebaceous

areas or in elderly skin with less sebum production, the skin is prepared with alcohol. 5-ALA is then crushed and shaken for 3 minutes to completely dissolve the drug powder in the solution vehicle. With the applicator end of the stick, the ALA is painted on the entire treatment area in 2 coats. The first coat is allowed to dry for 1 minute before the second coat is applied. Care is taken to avoid applying the product in the periorbital region (ie, <1 cm from the eyes). The ALA is incubated, without occlusion, in the office, for 1 to 6 hours, depending on the site. The patient then washes the treated area with water. We confirm the photoactivity of the photosensitizer by visualizing its fluorescence with a Wood light (Figure 2). To activate the ALA, an FDA-approved blue light–emitting diode (LED) device delivers 10 J/cm^2 of blue light to the treatment area for 16 minutes and 40 seconds while the patient wears protective goggles and a fan blows air onto the skin to alleviate discomfort. (Other light and laser devices can be used to activate PpIX.) The standard distance of the patient from the blue light source is 2 to 4 in.[13] If the device is placed further away, the total light activation dose is decreased. However, a patient may feel uncomfortable with the device placed too close, especially if the device completely surrounds the head (Figure 3). In that case, we increase the exposure time to compensate. During the irradiation, the patient is closely monitored for any adverse effects. Posttreatment, the patient is instructed to wash the face gently with cool water and is given a sunscreen to apply. No patient leaves our office without having applied adequate sun protection. Our standard treatment protocol for AKs is for the patient to return in 4 to 6 weeks for a second treatment. In general, we note clearance in approximately 80% to 90% of AKs and AC after 2 consecutive sessions, spaced 1 month apart. In cases of AC, edema of the lip is common after PDT. In this case, incubation time is typically between 30 minutes and one hour. Use of a low-potency topical steroid ointment twice a day posttreatment for 1 week is very helpful. In severe cases, a short course of oral steroids is given.

PHOTOAGING

With age and environmental exposure (eg, UV light and smoking), patients accumulate visible damage, such as rhytides; redness and telangiectasias; pigmentary alterations (eg, lentigines); rough texture with keratoses (ie, actinic and seborrheic); and a coarse, sallow, lax appearance corresponding to loss of dermal collagen and lipoatrophy. While performing clinical studies of PDT for the treatment of AKs, we serendipitously noted that patients demonstrated improvement in the appearance of photoaging.[14] Although the exact mechanism of action of PDT in photorejuvenation is still unclear, the role it plays in antineoplastic and anti-inflammatory processes is important. An assortment of light sources (eg, IPL, blue LED, and PDL) have demonstrated efficacy in improving features for photoaging. We consider a combination of ALA-PDT and IPL an ideal treatment for photoaging. IPL emits a range of noncoherent, polychromatic light at wavelengths of 500 to 1200 nm and is used by dermatologists for the treatment of photodamaged skin and pigmentary and telangiectatic disorders.[15] Lately, several split-face clinical studies have demonstrated that the application of ALA prior to IPL treatment enhances photorejuvenation more than IPL alone (eg, improvement in telangiectasias, rhytides, pigmentation, skin texture, and keratoses).[16-18] This increased efficacy may be due to the increase in type 1 collagen production that is seen with PDT and IPL activation.[8,19] Erythema, edema, and exfoliation were also moderately

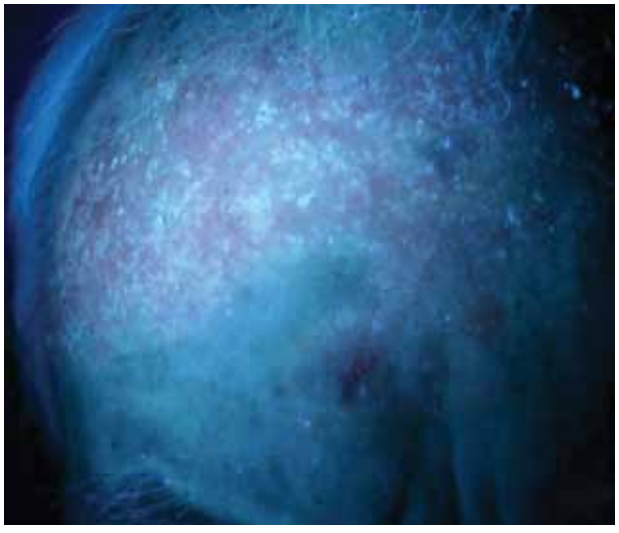

Figure 2. Wood light fluorescence of a photosensitizer.

Figure 3. Patient undergoing photodynamic therapy irradiation.

increased after the combined therapy, but there was no rise in complications reported.[8]

We use the following PDT treatment protocol for photoaging. Prior to initiating treatment with PDT, hyperkeratotic AKs are pretreated with various destructive methods (eg, liquid nitrogen and electrocautery). Patients who are taking retinoids are instructed to continue taking them up until the night before treatment but to stop taking them for 1 week after PDT to prevent further irritation. On the day that PDT is initiated, the patient is asked to wash the area of skin that is to be treated with a gentle cleanser and water. The skin is prepared with acetone only in patients with very oily skin or severe AKs. Otherwise, alcohol is used to prepare the skin. 5-ALA is crushed and shaken for 3 minutes to completely dissolve the drug powder in the solution vehicle. With the applicator end of the stick, ALA is painted on the entire treatment area in 2 coats, taking care to avoid applying the product in the periorbital region (ie, <1 cm from the eyes). The ALA is incubated, without occlusion, in the office for 30 to 60 minutes. The patient then washes the treated area with water. An IPL device with a 560-nm filter and an average fluence of 24 J/cm^2 is used to activate the treatment area while the patient wears protective goggles. During the irradiation, the patient is closely monitored for any adverse effects. Posttreatment procedures, described earlier, are performed, and the patient is instructed to return in 4 weeks for evaluation and, if necessary, retreatment. In general, we note a decrease in the total number of IPL treatments needed to achieve improvement in the signs of photoaging.

ACNE VULGARIS

Acne vulgaris is a common inflammatory disease of the pilosebaceous unit that has significant impact on the patient's quality of life and long-lasting negative consequences, such as scarring. Acne generally presents as comedones, pink to red folliculocentric papulopustules, and nodulocysts in the seborrheic areas. A vast range of topical and systemic therapies are available to treat acne (eg, retinoids, antibiotics, acid peels, and hormones); however, each treatment has its advantages and disadvantages. PDT using ALA with various light sources has been shown to be a safe, effective, and lasting alternative or adjunctive treatment for mild to severe acne.[20]

The pathophysiology of acne involves 4 main mechanisms encompassing hormonally induced sebaceous gland proliferation with an associated rise in sebum production, alteration of follicular development, abundance of *Propionibacterium acnes*, and inflammation. Interestingly, ALA-PDT exerts its therapeutic effect by diminishing these etiologic factors and improving scars.[20] Prior experimental studies show that the pilosebaceous unit selectively accumulates PpIX containing natural photosensitizing porphyrins in addition to *P acnes*.[20] Hongcharu et al[21] demonstrated a corresponding decrease in sebaceous gland sebum production and a decline in *P acnes* in the follicles after treating and improving acne in patients treated with ALA-PDT combined with a red light source. Although a variety of light sources were evaluated when combined with ALA-PDT for the treatment of acne, PDL was found to be the most efficacious, possibly because of its ability to destroy perifollicular blood vessels.[22] In addition, ALA-PDT, in combination with various light sources, appears to be more successful in treating inflammatory, moderate to severe acne than comedonal acne.[22] Even though most of the adverse effects of ALA-PDT are similar to those occurring with other indications when used for acne, there are a few reports of patients with acne who developed severe papulopustular flares after ALA-PDT therapy; hence, the possibility of this rare adverse event must be discussed with patients during pretreatment counseling.[20]

The ALA-PDT treatment protocol that we use as adjunctive therapy for acne at the University of Miami is as follows. The patient washes the skin area that is to be treated with a gentle cleanser and water. Patients who are taking retinoids for their acne are instructed to continue taking them up until the day of treatment but to stop taking them for 4 to 7 days following treatment. The face is prepared with an acetone scrub. 5-ALA is crushed and shaken for 3 minutes to completely dissolve the drug powder in the solution vehicle. With the applicator end of the stick, ALA is painted on the entire treatment area in 2 coats, taking care to avoid applying the product in the periorbital region (ie, <1 cm from the eyes). The ALA is incubated, without occlusion, in the office for 30 to 60 minutes. The patient then washes the treated area with water. A blue LED at 415 nm is used to activate the ALA. In cases of nodulocystic acne, a red LED at 633 nm is used, as penetration is deeper with this wavelength and efficacy is improved. The patient wears protective goggles, and an adjacent fan blows air onto the skin to alleviate discomfort. During the irradiation, the patient is closely monitored for any adverse effects. Posttreatment, the patient is followed up in 2 weeks for evaluation and, if necessary, retreatment. Typical treatment regimens involve 2 sessions with ALA-PDT spaced 2 weeks apart, followed by blue light exposure without ALA twice a week for 4 weeks.

HIDRADENITIS SUPPURATIVA

Similar to acne vulgaris, HS is a chronic and debilitating inflammatory disease of the follicular unit involving apocrine-bearing skin (ie, the axillae and groin and the

gluteal, inframammary, and periumbilical areas), affecting approximately 1% of the US population.[23] The manifestation of HS includes pink to red follicular papulopustules and nodules that gradually develop into purulent abscesses, sinuses, and fistulas, leading to significant scarring and long-term impairment. Although there are a number of available therapies to treat HS (eg, antibiotics, corticosteroids, hormones, retinoids, and biologics) along with surgical interventions, these are imperfect and often exasperating to patients. The precise mechanism of action of PDT for HS is uncertain, except for the fact that it resembles PDT's mechanism of action for a similar acneiform condition, acne vulgaris. The collection of PpIX in the follicular unit and the anti-inflammatory effect likely contribute to PDT's effectiveness in HS.[20] Recently, a case series indicated the safety and durable efficacy of ALA-PDT combined with blue light for treating HS.[24]

The PDT treatment protocol that we utilize at the University of Miami for HS is as follows. The patient washes the skin area that is to be treated with a gentle cleanser and water. The area is then prepared with acetone, unless there are open cysts, in which case acetone is avoided. 5-ALA is crushed and shaken for 3 minutes to completely dissolve the drug powder in the solution vehicle. With the applicator end of the stick, ALA is painted on the entire treatment area in 2 coats. The ALA is incubated, without occlusion, in the office for 30 to 60 minutes. The patient then washes the affected area with water. Blue light or red light is then used to activate the ALA while the patient wears protective goggles and an adjacent fan blows cool air to alleviate discomfort. We use a combination of red and blue light on subsequent visits; each affords its benefits, as blue is the best activator of PpIX, but red offers better penetration. During the irradiation, the patient is closely monitored for any adverse effects. Typical treatment protocols for HS include 2 treatments of ALA-PDT spaced 1 to 2 weeks apart, followed by twice-weekly alternating treatments with blue LED then red LED for a total of 8 treatments. Our regimen for HS is similar to that for acne except that the first several visits are sometimes spaced further apart to allow for healing of the treated intertriginous areas.

VERRUCA VULGARIS

VV is a common benign growth that often presents in children and immunosuppressed individuals (eg, HIV and transplant patients) and is caused by infection with the human papillomavirus. Because of its potential to spread rapidly, causing cosmetic, physical, and psychological problems, as well as its potential to transform into squamous cell malignancies in immunodeficient patients, VV is an important disease to remedy.[25] However, managing this condition is challenging for clinicians and frustrating for patients because the warts are often resistant to treatment (eg, cryotherapy, electrosurgery, PDL, and topical acids). Therefore, a novel therapeutic armamentarium that includes PDT is being developed. Since 1995, multiple clinical studies have revealed the safety and efficacy of using ALA-PDT with different light sources to treat minimal to diffuse VV in various skin locations.[25] For deeper penetration through hyperkeratotic warts and, therefore, better efficacy, some investigators have added pretreatment paring, occlusion, or both during incubation. One recent study demonstrated a 100% cure rate of VV using ALA-PDT and PDL therapy, an efficacy level that was probably partly due to the antivascular properties of the laser.[26] The mechanism of action of PDT in treating VV is still unclear, yet its efficacy is likely derived from amassing PpIX in atypically growing, human papillomavirus–infected cells that are selectively targeted and destroyed.[27] One important downside to PDT as a treatment for warts, especially in the pediatric population, is the considerable pain experienced by the majority of treated patients.[27]

The following PDT protocol is used at the University of Miami for recalcitrant VV. The patient washes the skin area that is to be treated with a gentle cleanser and water. For hyperkeratotic warts, we either pretreat them with keratolytic agents prior to the treatment visit or pare them immediately prior to ALA application. 5-ALA is crushed and shaken for 3 minutes to completely dissolve the drug powder in the solution vehicle. With the applicator end of the stick, ALA is painted on the entire treatment area in 2 coats. The ALA is incubated, without occlusion, in the office for 1 to 3 hours. The patient then washes the treated area with water. A PDL (585 nm or 595 nm) is used for activation. We operate the long PDL at 595 nm with an average fluence of 11.5 J/cm^2 and a 1.5-ms pulse width off face and an average fluence of 9 J/cm^2 on face. For flat warts, the fluence is lowered to 8 J/cm^2. During the irradiation, the patient is closely monitored for any adverse effects. Posttreatment procedures are conducted next, and the patient returns in 3 to 4 weeks for evaluation and, if necessary, retreatment. As with any treatment modality for VV, multiple sessions are required for complete resolution (Figure 4).

SUMMARY

PDT is a developing and dynamic management option for many dermatologic disorders. By selectively targeting abnormal tissue, PDT is capable of eliminating neoplastic, infectious, and inflamed cells while leaving nearby normal tissue unharmed. The benefits of PDT include its ease of use, its short associated downtime, and a good safety and efficacy profile. Its shortcomings include procedural discomfort and potential phototoxicity. In this

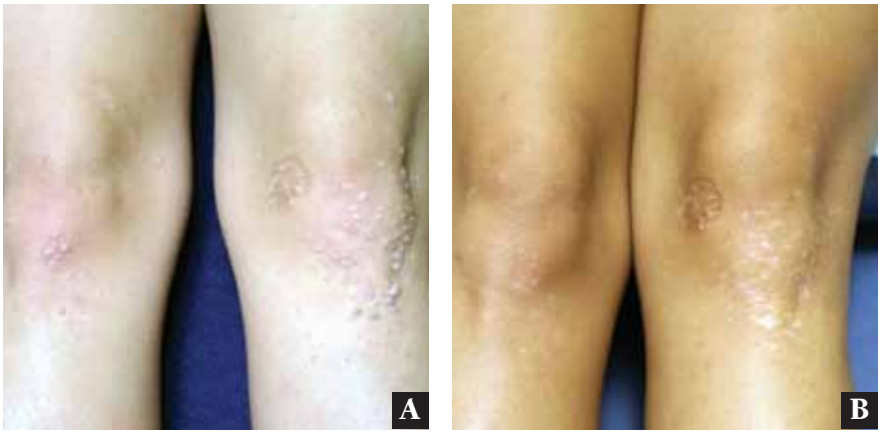

Figure 4. Widespread verruca vulgaris on a patient's legs before (A) and 2 months after (B) photodynamic therapy consisting of 3 treatments with 5-aminolevulinic acid and long pulsed dye laser incubation.

overview, we have discussed the background of PDT and its mechanisms of action, as well as the PDT protocols used to treat AK, AC, photoaging, acne, HS, and VV at the University of Miami (Table). Although the scope of knowledge and application of PDT are in their formative years, numerous studies are under way to further elucidate and enhance the role of PDT in dermatology.

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