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Dermatol Clin 25 (2007) 101–109

DERMATOLOGIC
CLINICS

Photodynamic Therapy: Other Uses

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Mainstream uses for photodynamic therapy (PDT) in dermatology include nonmelanoma skin cancer and its precursors, acne vulgaris, photorejuvenation, and hidradenitis suppurativa. Each one of these entities and more is covered elsewhere in this issue. Many other dermatologic entities have been treated with PDT and published in the literature. These include psoriasis vulgaris, cutaneous T-cell lymphoma (CTCL), disseminated actinic porokeratosis (DSAP), localized scleroderma, and vulval lichen sclerosus (LS). Nondermatologic applications include anal and vulvar carcinoma, palliation of metastatic breast cancer to skin, Barrett's esophagus, and macular degeneration of the retina. These are divided in the following categories and the literature explored in each: nonmelanoma skin cancer, other neoplasia (dermatologic and nondermatologic), inflammatory/immunologic, infectious, and miscellaneous (Table 1).

Nonmelanoma skin cancer

Actinic keratosis, basal cell carcinoma, and squamous cell carcinoma are reviewed elsewhere.

Disseminated superficial actinic porokeratosis

This condition is a clone of actinically damaged cells that have the potential to transform into squamous cell carcinoma; hence, the author chose to put DSAP in this category. The general consensus anecdotally is that PDT is not effective for DSAP; however, only one paper, which treated three patients with topical PDT, is in the literature and the investigators failed to get a response [1]. The author has treated three patients for DSAP with success (unpublished observations). One patient is a 55-year-old woman who had widespread DSAP (legs, arms, back) who had two lesions convert into histologically proven squamous cell carcinoma. She had been treated with imiquimod and 5-flourouracil topically over many years, but developed systemic side effects from both. She has responded well to multiple PDT sessions with 20% aminolevulinic acid (ALA) solution (Levulan, DUSA Pharmaceuticals, Wilmington, Massachusetts). In the author's experience, DSAP can be treated with PDT successfully; however, multiple treatments are necessary at the highest light dosages and longest incubations with some pretreatment of the lesions (5-fluorouracil, imiquimod, salicylic acid containing compounds, retinoids, or a combination thereof). This does clear many of the lesions, which will reoccur over the next 1 to 2 years, and leads to the possibility that annual treatments may be necessary. It is hoped that more case reports and clinical trials will be reported in the future to add to our knowledge of how to treat this difficult disease.

Inflammatory/immunologic disorders

Acne vulgaris and hidradenitis suppurativa are covered elsewhere in this issue.

Neither grants nor subsidies were received to prepare this manuscript. The author is a consultant to DUSA pharmaceuticals. Receipt of honoraria for educational activities has been received in the past. The author owns a small amount of stock in DUSA. She also is on the Board of Directors for the American Society for Photodynamic Therapy.

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0733-8635/07/$ - see front matter
doi:10.1016/j.det.2006.09.007

Table 1
Conditions treated by photodynamic therapy

Nonmelanoma skin cancer	Other neoplasia	Inflammatory/immune disorders	Infectious disorders	Miscellaneous
Actinic keratosis[a]	Dermatologic	Acne vulgaris[a]	HPV[a]	Laser-assisted hair removal
Basal cell CA[a]	Cutaneous T-cell lymphoma	Psoriasis	MRSA	
		Lichen planus	Osteomyelitis	
Squamous cell CA[a]	Nondermatologic	Lichen sclerosus	Molluscum contagiosum	
Actinic cheilitis[a]	Vulvar/cervical intraepithelial neoplasia	Scleroderma	Tinea rubrum	
DSAP	Anal carcinoma	Alopecia areata	Oral candidiasis	
	Penile intraepithelial neoplasia	Darier's disease		
	Barrett's esophagus	Hidradenitis suppurativa[a]		
	Breast cancer metastatic to chest wall	Macular degeneration of the retina		

Abbreviations: CA, carcinoma; HPV, human papillomavirus; MRSA, methicillin-resistant *Staphylococcus avreus*.
[a] Not covered in this article; covered in depth in other articles in this issue.

Psoriasis vulgaris

There is a fair amount of literature devoted to the treatment of psoriasis vulgaris with PDT; outcomes are mixed about whether PDT is a practical or useful alternative for treatment.

The first hurdle was to demonstrate the mechanism of action of PDT or preferential uptake of a photosensitizer by psoriatic plaques. Bisonnette and colleagues [2] looked at the potential for specificity of oral ALA in dosages of 10, 20, and 30 mg because they believed that using topical PDT would be too limiting. They measured 12 patients with plaque psoriasis' protoporphyrin IX (PpIX) fluorescence in the lesional and normal skin as well as in inflammatory cells. There was a 10-fold increase in fluorescence at 3 to 5 hours after administration of a single oral dose in the psoriasis over the normal skin, although they did note some fluorescence of noninvolved facial skin. They concluded that this was a modality that warranted potential study for clinical usage. An earlier study [3] had established that PDT with red light caused a similar, although less potent, decrease in cytokine secretions (interleukin [IL]-6, tumor necrosis factor [TNF]-α, IL-1β) as did psoralen plus ultraviolet A light (PUVA) therapy in mononuclear cells that were isolated freshly after irradiation with either modality. It also demonstrated progressive photobleaching corresponding to higher energy irradiations, which established the specificity and dose dependency for PDT for psoriasis vulgaris. A recent study showed that systemic PDT induces apoptosis in lesional T lymphocytes in psoriatic plaques, a feature that is supposed to predict a longer-lasting therapeutic effect [4].

With some evidence of a mechanistic reason and proof of some specificity for psoriasis vulgaris, small clinical trials were instituted to test whether this was borne out in a clinical setting. Ten patients who had plaque psoriasis [5] were treated multiple times at thrice a week dosing with topical application of 5-ALA and broadband visible radiation at dosage of 8 J/cm^2. Eight out of ten patients showed a clinical response, but only 1 of 45 sites cleared fully and 5 showed no improvement. More concerning was that fluorescence, which was demonstrated by biopsy to remain in the epidermis, showed little consistency of uptake, even within the same plaque. Finally, there was so much discomfort with the treatments that the investigators concluded this was not a practical therapy.

Three studies in 2005 shed new light on the clinical evaluation of PDT for psoriasis vulgaris. Twelve patients (8 evaluable) were studied for their response to topical 5-ALA 20% solution irradiated with red light weekly at 10 to 30 J/cm^2 [6]. There was a statistically significant improvement in the clinical presentation of the plaques; however, there was an average pain score of 7 on the Visual Analogue Scale and 4 of 12 patients dropped out of the study because of pain during

the treatments. A larger study was performed by the Regensberg, Germany group; 29 psoriatics who had chronic stable disease received 1% ALA after keratolytic treatment (10% salicylic acid in petrolatum for 2 weeks) in three plaques and 5, 10, or 20 J/cm^2 of a filtered metal halide light (Waldmann 1200 PDT, 600–740 nm) [7]. Although they demonstrated a clear decrease in the psoriasis severity area index score in more than 95% of patients, the slow pace, pain during therapy, and partial results were cited by the investigators as reasons for the inadequacy of this form of PDT for psoriasis vulgaris. They concluded that a more practical method might be oral ALA and blue light or verteporfin and red light. Finally, in a recent study, 8 patients who had symmetric plaques were studied for clinical response and immunohistochemical markers in a randomized, placebo-controlled study in which the patient's contralateral plaque served as control [8]. Ten percent ALA ointment under occlusion was used on one plaque, whereas the vehicle alone was used on the contralateral plaque; both were occluded for 4 hours and exposed to fractionated broadband light (Waldmann PDT 1200 L, 650–700 nm) at 2 J/cm^2, then 2 dark hours, followed by 8 J/cm^2. The PDT-treated side exhibited a clinical improvement and a decrease in CD4$^+$, CD8$^+$, and CD450RO cells as well as Ki67$^+$ nuclei, with an increase in epidermal K10 expression. These biologic changes were absent in the placebo-treated sides. Heterogeneity of plaques in fluorescent staining still was seen as an obstacle to practical therapy, and this was despite pretreatment with a salicylic acid–based cream to induce keratolysis. Still, despite a modest clinical result, the investigators hold out hope that protocols could be optimized for psoriatic therapy.

Psoriasis treatment for PDT seems to be limited by pain, inconvenience, and mediocre results. Clearly, it is not a first-line therapy; however, there is good evidence that there is preferential uptake of photosensitizers in psoriatic plaques and confirmation by biologic markers that specific antipsoriatic changes take place during PDT. Therefore, it is hoped that there will be a way to optimize PDT protocols for the treatment of psoriasis.

Lichen planus

There is only one reference, a recent study in the use of PDT, for the treatment of oral lichen planus (OLP). Twenty-six lesions of OLP were treated with gargling 5% methylene blue and subsequent irradiation with 632-nm laser at 120 J/cm^2. Significant symptoms and signs were decreased at 1 and 12 weeks in 16 lesions; the investigators concluded that this was a promising treatment for control of OLP [9].

Lichen sclerosus

This entity is mentioned twice in overviews of PDT and once by Polish investigators who stated they use PDT for diagnosis and treatment of LS; however, the full text could not be obtained and there were no details in the abstract [10].

Scleroderma

Patients who had localized scleroderma that was resistant to PUVA did respond well to PDT [11]. Cultured keratinocytes that were subjected to PDT produced increased IL-1, TNF, and matrix metallopreoteinase-1 and -3; these were postulated by the investigators to be the mechanisms that are responsible for the observed antisclerotic effect of PDT [12]. This observation needs to be repeated and is contrary to what is found clinically with photodynamic photorejuvenation (ie, fine wrinkles tend to get better and there has been no evidence of collagen breakdown). Another study, however, found a dosimetry range to reduce tissue contraction and reduce collagen density without damage to keratinocytes, which may prove helpful as an adjuvant treatment for keloids [13].

Alopecia areata

Six patients who had severe alopecia areata were treated with 5% to 15% ALA solution twice weekly for 20 treatments with red light. Fluorescence microscopy revealed diffuse uptake in the epidermis and sebaceous glands, but not in hair follicles or the inflammatory infiltrate surrounding the epidermis. Also, a significant degree of erythema was noted in all ALA-treated sites but not in the control site, which indicated that there was a clinical response to ALA. The investigators concluded that PDT is not a successful therapy for alopecia areata [14].

Darier's disease

A small pilot study of six patients was treated with 5-ALA; they also were taking systemic retinoids. One patient could not tolerate treatment. Of the other five patients, four had an

inflammatory response that lasted for 2 weeks, but it was followed by improvement that lasted from 6 to 36 months. There was recurrence in one patient; however, in those who were clear, biopsy was negative after treatment [15].

Macular degeneration of the retina

Macular degeneration of the retina occurs as an age-related phenomenon when new vessels under the retina proliferate and leak, which causes distortion and scarring and leads to reduction of visual acuity, and, ultimately, blindness. Use of PDT for this condition has made a previously untreatable disease treatable. Verteporfin is used as the photosensitizer; it is followed by a series of three to six treatments over 1 to 2 years, which results in a decrease of loss of vision relative to untreated controls, and, in some instances, an improvement of vision. This was approved by the US Food and Drug Administration in 2000 and has been used in more than 1 million applications [16].

The mechanism of action is induction of apoptosis in the endothelial cells in the proliferating vessels, which is specific and leaves the rest of the retina intact [17]. Investigators in this area disagree on whether PDT is appropriate in late-stage disease. In one study, 8 of 10 patients lost less than three lines of vision over 2 years in late disease [18]; however, in another study, many of the patients who had advanced disease had significant side effects after usage [19]. A Cochrane analysis of the literature concluded that PDT is safe and effective for treatment of macular degeneration of the retina, although the size of the effect is not understood completely [20]. There is a newer alternative therapy that involved injection of the drug anecortave acetate. In a recent comparative study this was shown to be about as effective as PDT [21].

Other neoplasia: dermatologic

Cutaneous T-cell lymphoma

Traditionally, treatment of early CTCL has been accomplished with PUVA, electron beam radiation, nitrogen mustard, and even topical steroids. It seems a logical consequence that PDT might be effective for CTCL because it is effective in other neoplasias of skin. Many pilot studies and cases report positive findings, although no large-scale studies have been reported. The first reported treatment of CTCL was in 1994, when two plaque lesions were treated with 20% ALA in water-in-oil–based cream, and incubation for 4 to 6 hours followed by laser irradiation [22]. PpIX production was demonstrated by real-time laser-induced fluorescence to have a fivefold increase in lymphoma cells over normal cells. In 1995, Oseroff's group hypothesized that activated lymphocytes ($CD71^+$) would accumulate PpIX preferentially because of their lower intracellular iron levels and because of competition for iron between ALA-induced heme production and cellular growth processes [23]. They demonstrated that incubation of ALA with the CD71 positive lymphocytes from a patient with Sezary syndrome was killed preferentially over normal, unstimulated lymphocytes, which indicated a possible mechanism for PDT as well as specificity for CTCL and potential for good clinical outcomes.

In 1999, Eich and colleagues [24] reported two cases, one of an uncommon type and location of CTCL (medium-large size pleiomorphic cells, $CD8^+$, $CD30^-$, ear) that had not responded to PUVA, interferon-α, or retinoid therapy, but achieved a histologically confirmed partial remission with PDT and subsequent complete remission (CR) with radiotherapy. A second patient had PDT to the eyebrow and the foot in combination with other modalities to effect a CR. In 2000, Orenstein and colleagues [25] presented two patients who had stages I and III CTCL. In stage I CTCL, lesions exhausted fluorescence 1 hour after irradiation and showed a good response with 170 J/cm^2. With the stage III lesion, fractionated dosages were necessary, with a total dose required of 380 J/cm^2. All six lesions responded well. Other case reports include successful treatment of a patient who had two isolated plaques [26] and a patient infected with HIV who had CTCL and achieved CR after two PDT treatment cycles [27].

In the largest study to date, Ros' group in Sweden examined 10 patients with 10 plaque and 2 tumor-stage lesions [28]. They also looked at histologic and immunohistochemical markers of the lesions. The protocol was 20% ALA, incubating for 6 hours, followed with red light. Complete clinical remission was noted in 7 of 10 plaques after a single treatment, with corresponding regression of infiltrate with markedly fewer proliferating cells and a decrease in Ki-67 and CD71. The tumor lesions did not respond. The investigators concluded that there was good clinical and histologic effect of PDT on local plaque CTCL.

In summary, the literature demonstrates a good response to PDT for localized plaque

CTCL, stage I in case reports and limited pilot studies, which were confirmed clinically, histologically, and by way of immunohistochemistry. A plausible mechanism for action and specificity has been postulated and demonstrated partially. Further large-scale studies are necessary to evaluate whether PDT will be useful in treating early CTCL, but it certainly would be warranted if other modalities had failed or if circumstances preclude patients from receiving other, more established, modalities.

Other neoplasia: nondermatologic

Any epithelial cancer or precursor lesion that is accessible to light irradiation can be treated with PDT. Mucous membranes are especially well-suited to PDT because of the increased permeability in the absence of a well-developed stratum corneum. Thus, vulvar, cervical, and anal carcinomas have been treated by PDT with some success.

Vulvar intraepithelial neoplasia

Vulvar intraepithelial neoplasia (VIN) grades I–III was treated with 20% solution of 5-ALA and treated with 100 J/cm^2 of laser light at 635 nm in 25 patients who had 111 lesions. Complete response was noted in 13 patients (52% who had 27 lesions. All patients who had VIN grade I and monofocal or bifocal VIN grades II–III showed complete clearance. Multifocal VIN grades II–III lesions were cleared only 27% of the time. The investigators concluded that PDT was a good alternative for VIN grades I–III uni- or bifocal disease, whereas multifocal, pigmented, and hyperkeratotic lesions were not amenable to clearance. Advantages of PDT include excellent cosmesis and function with minimal morbidity; disadvantages include the need for close surveillance of recurrence [29].

In another study, 22 patients who had VIN grades II–III had 10% 5-ALA applied for 2 to 4 hours and 80 to 125 J/cm^2 light at 635 nm. This was compared with CO_2 laser and surgical excision for VIN grade III. The complete response rate for VIN proven by biopsy was 57%. Reduced disease-free survival was related to multifocal lesions, regardless of therapy type. PDT was concluded to be as effective as conventional therapy, but it had shorter healing times and better cosmetic results [30].

A different photosensitizer, meta-tetrahydroxyphenylchlorin, in VIN grade III was injected intravenously (IV) at 0.1 mg/kg body weight and irradiated 96 hours later with a 652-nm diode laser. Patients healed without incident except for two cases of severe pain that lasted for 2 weeks and one case of cellulitis. At 6 months, two patients developed recurrence and one had a new site; all were retreated with PDT. At 2 years, there were no recurrences at the original site, and cosmesis and functional anatomy were preserved well [31].

Cervical intraepithelial neoplasia

Similar findings, albeit with less confirmatory studies, exist for cervical neoplasia and PDT. A recent comparison of PDT plus topical 5-ALA with cold-knife conization yielded similar clearance rates (75%) of human papillomavirus (HPV) at 3 months and disease-free rates at 12 months (PDT, 91%; cold-knife, 100%). PDT preserved the function and structure of the cervix better than did surgery; however, the investigators warned that close long-term follow-up is warranted [32]. Another study of 3% ALA in gel incubated for 3 hours with loop excision performed 3 months after PDT in 12 patients found no significant difference between PDT and placebo [33].

In a larger and more recent study, 105 patients who had CIN received Photofrin, 2 mg/kg IV, and were treated with a laser at 630 nm at 100 J/cm^2. CR was 90% at 3 months and 72% at 12 months, with eradication of HPV in 75%. Three patients required surgery 2 to 4 years after the PDT. The investigators concluded that this is an effective method for the treatment of CIN [34].

Penile intraepithelial neoplasia

Penile intraepithelial neoplasia (PIN) is difficult to treat and can require mutilating surgery. Ten patients who had PIN were treated with PDT. Two of 10 patients were cured with four or five treatments. Patients required a penile block to be able to tolerate the pain of the procedure; 50% of them had concurrent HPV-16, whereas 30% had LS. None of the patients was circumcised. The investigators concluded that prevention (circumcision) is better than treatment; however, even with only a 20% response rate this may be an alternative to mutilating surgery [35].

Anal carcinoma in situ

Anal carcinoma in situ is another mucosal surface cancer that is accessible to PDT. Twelve patients who had active HIV and high-grade

dysplasia of anal mucosa were given oral δ-ALA and light irradiation. All patients had a downgrading of dysplasia on follow-up at 5 months as measured by Papanicolaou smears. The investigators conclude that this is a useful treatment alternative to surgery in anal carcinoma in situ [36]. In another study, 13 patients were treated with oral ALA and IV Photofrin with a 633-nm diode laser treatment. Patients required 2 days of anesthesia and no sun, 2 weeks of hospitalization, and 8 weeks to recover. Eight of 13 patients had a complete response and were able to avoid disfiguring surgery [37].

In conclusion, CIN and VIN seem to be treated well with PDT if the lesions are not multifocal, pigmented, or hyperkeratotic as long as rigorous long-term follow-up is maintained and biopsies do not demonstrate invasive cancer. In addition, cosmesis and function are better preserved with PDT than with surgical treatments or destructions. Penile and anal carcinomas are much more difficult to eradicate; the treatments have long recoveries and are extremely painful with results that are not as good, but they may be warranted because the alternatives are mutilating surgeries.

Barrett's esophagus

The treatment of Barrett's esophagus, a precancerous/in situ lesion of the epithelial lining, had been on two extreme sides: periodic endoscopy with focal resections or total esophagectomy. PDT has become an important alternative, with varying degrees of success for low-grade and high-grade dysplasia. Twenty-six men who had mainly low-grade dysplasia were randomized to receive focal ablation with an argon plasma coagulator or PDT with IV Photofrin and 630-nm laser. PDT performed superiorly in eradicating dysplasia, although both were able to shorten the duration of the lesions [38]. A recent long-term study demonstrated that 20 men who had high-grade dysplasia of the esophagus had good response to PDT [39]. A dose-response study demonstrated that higher-dose light resulted in better ablation of lesions, but with more complications (eg, stricture, esophagitis) [40].

Breast cancer metastatic to chest wall

Palliation of pain and reducing difficult wound care are the goals of treating breast cancer that is metastatic to chest wall, which occurs in 5% of patients who have breast cancer. Eighteen patients with more than 500 truncal metastases were treated with IV Photofrin and 630-nm diode laser. Follow-up was from 6 to 24 months, with 9 of 14 complete responses; some tumors that were greater than 2-cm thick responded. The investigators concluded that this is a worthwhile treatment for palliation with excellent clinical response [41].

Infectious disorders

There is evidence that PDT can be active against bacteria, viruses, and fungi.

Bacteria

In 1990, it was demonstrated that *Escherichia coli* could be killed if pretreated with methylene blue and exposed to white light [42]. *Helicobacter* infection was eradicated with methylene and toluidine blue, using a copper vapor–pumped dye laser on ex vivo samples of ferret gastric mucosa, without damage to the underlying mucosa [43]. A novel porphyrin-based photosensitizer, XF73, showed high efficacy at killing methicillin-resistant *Staphylococcus aureus* (MRSA) without damage to keratinocytes or eukaryotic cells [44]. The investigators postulated a use for this photosensitizer to prevent MRSA infection in hospitals as well as for burns or other open wounds [45]. Mice that were infected with bacteria were saved from sepsis and had improved wound healing after PDT [46]. In other mouse studies, third-degree burns were treated with PDT; 98% of the bacteria were eradicated after one session [47]. Fifty-three percent of 19 mice that were infected with *Vibrio vulnificus* at a bacterial inoculation 100 times the lethal dose for 50% survived after being treated with 100 μg of toluene blue and red light (150 J/cm^2) [48]. *Staphylococcus aureus*–infected mouse bone was treated with PDT successfully [49]. This in vivo animal model was used to postulate that PDT might be a good therapeutic alternative for the treatment of osteomyelitis.

Fungi

PDT was shown to have in vitro effects against *Tinea rubrum* at dosages of ALA of 1 to 10 mmol and 10 to 14 days of incubation [50]. Diode laser was effective in activating toluene blue–induced PDT of *Candida* species at low levels [51]. Mice that had severe combined immunodeficiency developed mucocutaneous candidiasis that was treated successfully with methylene blue and 664-nm diode laser in a dose-dependent fashion. This led the investigators to conclude that this

could be a viable treatment options for humans [52]. Interdigital tinea pedis was treated successfully with 29% ALA in Eucerin cream and 75 J/cm^2 red light. The control group (light alone or ALA alone) had no response; however, four of nine patients had recurrence of disease within 4 weeks of therapy [53].

Viruses

The most literature on viral diseases that are treated with PDT regards warts or condylomata (also see elsewhere in this issue). Other viruses that were reported to be treated with PDT include molluscum contagiosum [54] and herpes simplex [55,56]. Other uses of PDT include inactivating pathogens from blood products before infusion [57].

In summary, PDT was shown in vitro and in animal models to be highly effective for various pathogens, including MRSA and candidiasis, in immunocompromised hosts. The varied organisms that were tested do not seem to be capable of mounting a defense or developing resistant strains to PDT. In addition, photosensitizers continue to be discovered that are specific to the pathogenic targets and are not mutagenic. Localized skin infections, chronic wounds, or oral candidiasis probably is the most convenient targets for PDT [57]. PDT shows great promise as a weapon against MRSA and other pathogens that easily develop resistance. This promise begs more research to transform PDT for anti-infective use from the exploratory phase to a clinical reality.

Miscellaneous

Hair removal

PDT was performed with ALA after cold wax epilation and a continuous-wave red laser. Hair removal was consistent with the amount of anagen hair present [58]. Alopecia presented as a side effect in a case report of treatment of Bowen's disease with 5-ALA and red laser light on an upper posterior arm. The tumor was eradicated after 2-years follow-up, but complete alopecia of the treatment area remained [59]. There are few data to support the use of PDT as an adjunct to laser hair removal, and there have been few reports of alopecia as a side effect of treatments. There has been no demonstration of specific uptake by hair follicle cells. The author has not found PDT useful anecdotally as an adjuvant for laser-assisted hair removal.

Overview of other uses of photodynamic therapy

PDT is useful in nonmelanoma skin cancers, immunologic and inflammatory disorders, neoplasias other than skin cancer, and infections. The ability of this treatment to hone in on dysplastic epithelial and endothelial cells while retaining viability of surrounding tissue is its key feature, because this leads to specific tumor destruction with cosmesis and function of the target organ intact. The ability of PDT to alter the course of immunologic and inflammatory diseases is in an exploratory stage, but one that is exciting to behold and certainly is well established for diseases of sebaceous glands, and, possibly, apocrine glands. Finally, the demonstration that PDT is capable of killing various pathogens without induction of resistance could make it an important treatment modality in this arena in the future.

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