Cosmetic Clinical Indications for Photodynamic Therapy

Amy Forman Taub, MD

Photodynamic therapy (PDT) arose as a method for treating actinic keratosis (AK) but also demonstrated a conspicuous side effect: beautification of the skin through rejuvenation of photodamage. Photodynamic photorejuvenation has become a common tool for the aesthetic physician, yet it still is underutilized for the treatment of conditions such as acne, enlarged pores, rejuvenation, and sebaceous gland hyperplasia (SGH), as well as skin cancer prevention. Mechanisms of action and protocols will be discussed for treatment of these conditions. Options for photosensitizers, light sources, and incubation strategies also will be reviewed. Finally, new methods for enhancing treatment results such as microneedle-assisted dermal infusion for more confluent and vastly increased uptake of photosensitizers and pretreatment with infrared light (IR) for improving efficiency of production of protoporphyrin IX (PpIX) also will be presented.

Cosmet Dermatol. 2012;25:218-224.

Photodynamic therapy (PDT) arose as a way to identify and treat nonmelanoma skin cancer and its precursors. Most patients with actinic keratoses (AKs) as well as basal and squamous cell carcinomas have conspicuous signs of photoaging. In addition to being highly efficacious as a therapy for AKs and basal cell carcinomas, it also caused a beneficial side effect that was hard to ignore: improving signs of photoaging. It did not take long for physicians to realize that PDT could be utilized on its own to treat photodamage, both in addition to and in the absence of AKs.

WHY ADD PDT TO YOUR COSMETIC PRACTICE?

Photodynamic therapy is one of the best treatments of moderate to severe photodamage that does not include a fractional laser. Even the worst "meltdowns" of PDT (ie, complete epidermal exfoliation) have not resulted in reports of scarring. Photodynamic therapy is one of the best treatments of enlarged pores because it has specificity for sebaceous gland cells; it also is extremely beneficial for patients with oily rosacea. In my experience, PDT is the best procedural treatment of acne, and it also is a viable treatment option for sebaceous gland hyperplasia (SGH). Photodynamic therapy can be used to prevent skin cancer[1] while also achieving notable cosmetic results without the need for expensive equipment.

PHOTODYNAMIC REJUVENATION

In a 2002 study, Ruiz-Rodriguez et al[2] were the first to coin the term *photodynamic rejuvenation.* The authors combined AK treatment with an intense pulsed light (IPL) photorejuvenation procedure, which was known as efficacious for reducing the signs of photoaging, instead of using red or blue light. The study included 17 participants with a total of 38 AKs. Topical 5-aminolevulinic acid (ALA) 20% oil-in-water emulsion was applied to the AK lesions for 4 hours followed by IPL with 2 treatments with a 1-month interval. The treatment resulted in clearance of 33 (87%) of 38 lesions,

From Advanced Dermatology and Skinfo, Lincolnshire, Illinois, and Northwestern University Medical School, Chicago, Illinois. Dr. Taub is a consultant, researcher, and speaker for DUSA Pharmaceuticals, Inc, as well as a researcher and speaker for Syneron Medical Ltd.

Correspondence: Amy Forman Taub, MD, 275 Parkway Dr, Ste 521, Lincolnshire, IL 60069 (drtaub@advdermatology.com).

and the treated skin looked more luminous; however, the follow-up period was short and the cosmetic benefits were not quantified.[2]

Two subsequent groups conducted split-face comparisons of ALA-IPL versus IPL alone. Alster et al[3] evaluated 10 participants treated with 5-ALA and IPL on 1 side of the face and IPL alone on the contralateral side. The results for IPL in conjunction with 5-ALA were superior to IPL alone at 1, 3, and 6 months posttreatment.[3] Gold et al[4] evaluated 13 participants in a similar split-face design who showed superiority on the ALA-IPL–treated side of multiple photoaging markers, including crow's-feet (55% vs 29% improvement), tactile roughness (55% vs 29%), mottled hyperpigmentation (60% vs 37%), and telangiectasia (85% vs 54%).

There also have been studies investigating dermal changes associated with topical PDT. One study compared the results of methyl aminolevulinate (MAL)−PDT in mouse skin with controls of MAL alone and red light alone. Results from MAL-PDT revealed immediate increases of IL-1β, tumor necrosis factor α, transforming growth factor β1, and matrix metalloproteinases, along with delayed type I collagen synthesis.[5] In another study that evaluated ultrastructural changes following PDT, increases in type I collagen were greater on the ALA-IPL side versus the side treated with IPL alone.[6] Not only do these studies illustrate the efficacy of PDT in treating photoaging in the epidermis, but they also reveal that changes in the dermis may be just as profound.

The protocol that I follow for photodynamic photorejuvenation is a 30-minute incubation with ALA after cleansing with an electric brush (Clarisonic, Pacific Bioscience Laboratories Inc), acetone scrub, and alcohol wipe. Intense pulsed light usually is administered with an electro-optic synergy system (ELOS, IPL plus bipolar radiofrequency) using a skin rejuvenation advanced handpiece (eLight, Syneron Medical Ltd) with either 3 treatments spaced 1 month apart or 2 of 5 ELOS treatments with ALA. (The choice of light source and incubation time are discussed below.)

PDT FOR ACNE, SGH, AND ENLARGED PORES

Photodynamic therapy for the treatment of acne has been well-documented. Three US studies have demonstrated 70% to 100% improvement of acne when treated with ALA in combination with IPL or the pulsed dye laser (PDL).[7-9] Photodynamic therapy is one of the most underutilized acne treatments given its efficacy and the large number of patients with moderate to severe acne. However, PDT is not covered by insurance and is not approved by the US Food and Drug Administration (FDA) for the acne indication, thus entailing a substantial out-of-pocket expense. Patients also must stay indoors 48 hours posttreatment, which can be especially difficult for teenagers. Barolet and Boucher[10] suggested a modification that could make the treatment more affordable and/or practical. The study included 10 participants with at least 10 acne lesions who were treated with infrared light (IR)(970 nm) on one side of the face prior to incubation with ALA; PDT then was used on the entire face. The side pretreated with IR demonstrated a 73% improvement in acne lesions after only 1 treatment versus the side without IR, which demonstrated a 38% improvement.[10] This method could be considered as a possible single-treatment protocol. It also has been hypothesized that by using IR before treatment, red and/or blue light without a photosensitizer might be effective enough to treat acne. An unpublished phase 2b study showed no difference between blue light only and blue light with ALA in the treatment of acne; both methods demonstrated high efficacy (DUSA Pharmaceuticals, Inc, 2008). Treatment of acne with no photosensitizer would reduce the cost as well as increase the ease of use, as there would be no downtime and no period of photosensitivity; however, these hypotheses require further proof before they can be endorsed.

Sebaceous gland hyperplasia is difficult to treat. Most practitioners approach this condition with classic electrodesiccation,[11] but as we know, this method only flattens the lesion, while the dermal portion of the enlarged gland remains intact. Photodynamic therapy has been explored as an option to treat SGH and has been found to be effective.[12,13] I prefer to combine light electrodesiccation with PDT to reduce the number of treatments required for clearance (Figure 1).

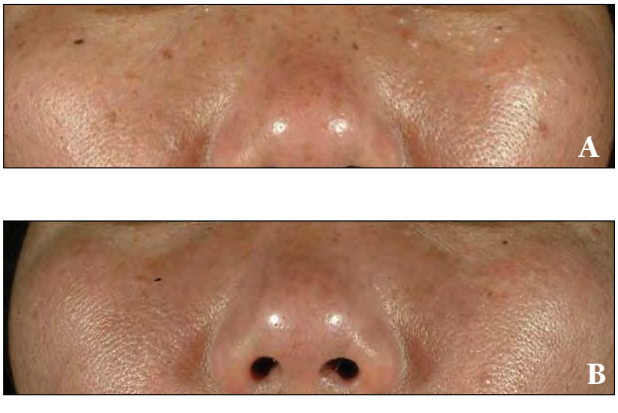

Figure 1. Before treatment (A) and after electrocautery and 2 photodynamic therapy treatments (1 with blue light and 1 with intense pulsed light plus radiofrequency [electro-optic synergy system])(B).

Enlarged pores are not considered to be a clinical condition but definitely are a concern for many patients. In a study of PDT with indocyanine green and an 810-nm diode laser, all 5 participants demonstrated a subjective improvement in pore size.[14] Enlarged pores have been shown to correlate with the male gender, acne, and reduced skin elasticity.[15] The association with decreased skin elasticity may explain why pores seem to enlarge with age. In one of the hallmark studies of PDT and acne, sebaceous glands were shown to be selectively destroyed by PDT.[16] Whether the effects are temporary or permanent, patients clearly need an effective treatment for a variety of conditions.

LIGHT SOURCES FOR PDT

No review of PDT would be complete without a discussion of the available light sources for activation of the photosensitizer of your choice.

Any light source or laser with a wavelength between 300 and 640 nm will activate protoporphyrin IX (PpIX), the actual photosensitizing molecule that is the by-product of the heme pathway when these photosensitizers are introduced exogenously, which includes UV, blue, red, and yellow light, as well as potassium-titanyl-phosphate, PDL, and IPL devices. Because much of the research has been with blue and red light, PDLs, and IPL, this review will focus on those light sources.

UV light is an extremely high-intensity activator of PpIX; however, dermatologists do not use this wavelength to fight sun damage because it is the principle cause of the damage. Blue light has been extensively used for treatment of AK because the peak absorption of PpIX occurs at this wavelength. Blue light typically can only penetrate depths of approximately 2 to 3 mm,[17] limiting the effectiveness of this wavelength to the epidermis and superficial dermis. On its own, blue light has antiproliferative,[18] antibacterial,[19] and anti-inflammatory[20] properties, but it has no effect on melanin or hemoglobin (ie, targets for photodamage). Although red light can reach depths of 4 mm (deeper dermis) and has some healing effects of its own,[21] it does not have a specific effect on pigmented keratinocytes. A recent study compared the efficacy of red versus blue light for photodynamic rejuvenation by using each in combination with MAL and measuring the improvement demonstrated by both treatments. Although both treatments were equally effective in rejuvenation, all participants also were treated with either PDL or IPL.[22] Without isolating only red or blue light alone, it is difficult to attribute improvement to either of these wavelengths. Much of the literature for PDT for photoaging has focused on IPL, and with good reason. Intense pulsed light alone treats telangiectasia, lentigines, sallowness, and superficial wrinkles. The literature includes split-face studies showing that ALA-IPL is superior to IPL alone. A newer photosensitizer has been utilized principally with red light for photoaging.

Photodynamic rejuvenation traditionally has been accomplished with IPL. It is possible that not all IPL devices could accomplish these results because most published studies were performed with 1 brand of IPL. I principally have used the ELOS form of IPL with similar but unpublished results. This particular device has shown results that are similar to another IPL when used without a photosensitizer[23] but not with one. A recent study with red light and MAL showed global improvement of all indicators of photoaging, except telengiectasia.[24] Another split-face study utilized MAL with red light for treatment of photoaging, for either 1 or 3 hours. Results showed that there were differences in fine lines, roughness, and tightness of the face, but there were no differences in telangiectasia or lentigines; the side receiving the 3-hour treatment was accompanied with more side effects but showed better results.[25] There may be some methods to amplify the conversion of endogenous porphyrins that could result in improved cosmetic results over red or blue light therapy alone.

PHOTOSENSITIZERS FOR PDT

There currently are 3 photosensitizers that are commercially available in the United States for PDT. The most tested and widely used product in the United States is ALA 20% in a hydroalcoholic, single-use applicator stick (Levulan Kerastick, DUSA Pharmaceuticals, Inc). Methyl aminolevulinate cream 16.8% (Metvixia, Galderma SA) is more widely used in Europe but has been available in the United States for a couple of years. Hexaminolevulinate 0.5% (Allumera, Photocure USA), an ALA hexyl ester, is a new product. It is considered a cosmetic and has not been submitted to the FDA for approval; however, a lower strength of the same chemical is FDA approved for enhancing visualization of bladder cancer during cystoscopy (Cysview, Photocure USA).

Aminolevulinic acid 20% was formulated for epidermal penetration and can be stored at room temperature; it is approved for the treatment of AK after 14 hours of incubation with blue light PDT (BLU-U, DUSA Pharmaceuticals, Inc) for 1000 seconds (16 minutes; 40 seconds=10 J/cm^2); however, it commonly is used at an incubation time of 1 to 3 hours for AK and sometimes as little as 30 minutes with IPL for photodynamic photorejuvenation. The rationale for these shorter incubation times comes from a study by Touma et al[26] that showed that 1, 2, and 3 hours of incubation were as efficacious as the 14 to 18 hours of incubation indicated for

the treatment of AK. The rationale for even shorter times is that the purpose of photodynamic photorejuvenation is to enhance cosmesis with less downtime; multiple treatments are acceptable to achieve the end point as long as the downtime is reduced.

Although there are many opinions in the field when each photosensitizer should be used, few head-to-head studies employ the commercially available photosensitizers in a way that could actually compare efficacy, and none for photorejuvenation. There are numerous variables that make it difficult to evaluate results in studies on PDT. Not only is the choice of photosensitizer a variable, but the length of duration of incubation, the presence or absence of occlusion, and the light source are all important. Also, each clinical indication has uniquely different targets. Although the strongest yet tolerable treatment would be desirable for treatment of skin cancer or precursors, a gentler cumulative approach would be better for the average patient with photodamage.

INCUBATION TIMES

The approved incubation time for MAL is 3 hours with occlusion and 14 to 18 hours for ALA. Both are approved for lesional but not full-field application. The majority of current PDT usage is as a field treatment. Most practitioners would agree that it is wasteful to use a costly disposable resource on just a few lesions when we know there is a high likelihood that subclinical lesions are present and photosensitizers are specific for actinically damaged cells. Short-contact field application was heralded into current thinking by the seminal study by Touma et al[26] revealing that a 1-hour incubation of ALA was just as efficacious as a 3-hour incubation and utilizing the photosensitizer in a field application. There are no studies specifically addressing a 30-minute incubation time for rejuvenation with PDT, though there are examples of studies utilizing 30-minute incubation times that achieved comparable results to other studies.[4] Two things have led me to utilize an incubation time of 30 minutes: (1) my own study of acne utilizing 15- to 30-minute incubation times[27] with good outcomes, and (2) my desire to have less downtime for patients seeking cosmetic improvements. There is a large population of patients who prefer to have multiple treatments with less downtime per session versus a single treatment that can produce similar results but has greater or more visible cosmetic morbidity. Hypothetically but not clinically proven, 30 minutes of incubation could yield positive cosmetic outcomes with less downtime compared with a 1-hour incubation period. A study of isolating AKs showed that 48% of treated lesions had a statistically greater fluorescence at 20 minutes of incubation than normal cells,[28] demonstrating that even this short incubation time can induce positive clinical effect.

METHODS FOR ENHANCING CLINICAL RESULTS OF PDT

There are 2 basic strategies to enhance the results of a given light source and PDT: (1) increase the absorption of the photosensitizer, or (2) increase the conversion of the photosensitizer to PpIX. Strategies to increase absorption include occlusion of the photosensitizer, longer incubation of the photosensitizer, use of topical therapies, microdermabrasion, or microneedling prior to treatment.

One basic strategy is occlusion of the photosensitizer during incubation. A recent PubMed search of articles indexed for MEDLINE using the terms *PDT and occlusion* did not turn up any articles specifically evaluating the effectiveness of this strategy. Methyl aminolevulinate's label calls for occlusion of the drug. Common sense certainly seems to suggest that occlusion would lead to increased absorption, though it does not appear to have been proven.

A longer incubation is another possible strategy for increasing absorption. Most studies have tended to focus on reducing the time of incubation, both to make the treatments more practical and to limit the side effects of therapy without compromising efficacy.

Pretreatment of the skin with topical therapy is another method for enhancing the results of PDT. The stratum corneum is the biggest barrier against absorption of any topically applied medication,[29] thus most employed strategies focus on diminishing this barrier. Reports of the use of topical retinoids[30] and 5-fluorouracil[31] for pretreatment mainly have been examined for improvement of efficacy in AK reduction. The use of retinoids is one method to presumably increase penetration via reduction of the stratum corneum barrier, whereas 5-fluorouracil would tend to increase penetration more specifically within the AK. Other studies have shown that microdermabrasion increases absorption and may reduce the need for longer incubations.[32] In contrast, pretreatment with urea did not increase the efficacy of AK treatment.[25]

One PDT enhancement centers on heating the targeted skin prior to incubation of the photosensitizer, which has been shown to increase the efficiency of generation of PpIX from precursors.[33] In the split-face study of patients with moderate acne who had 1 side of the face pretreated with IR (970 nm) and the other side not treated, the side that was pretreated with IR showed an almost 2-fold improved clearance over the nonpretreated side, presumably because of the heat generated from the IR.[10]

Another interesting enhancement method is microneedling[34] prior to PDT. Microneedling involves the use of a roller with titanium or stainless steel needles to make 0.2- to 0.3-mm holes across the epidermis to enhance absorption of the photosensitizer (Figure 2). This procedure results in a uniform uptake of the photosensitizer and PpIX (Figures 3 and 4), which could lead to increased rejuvenation effectiveness, as it is less dependent on uptake by abnormal cells. It also might lead to better results per treatment. None of these benefits has been definitively documented in a study; however, one study demonstrated that this method does not increase erythema or pain.[35] The Clementoni et al[34] study also obtained impressive clinical results.

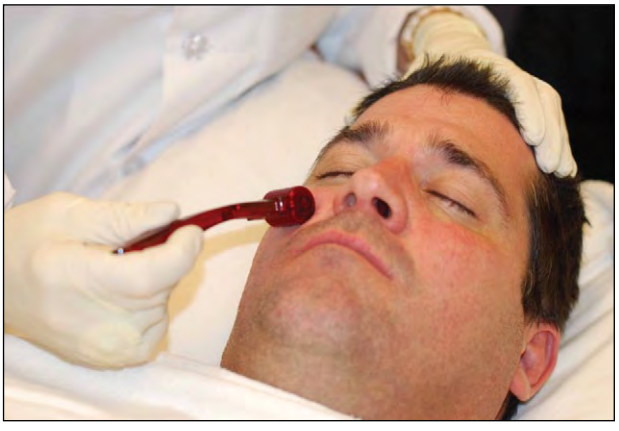

Figure 2. Microneedle-assisted dermal infusion.

In a study of pig skin,[36] an ablative CO_2 laser was administered before application of MAL for 3 hours, and a statistically significant difference was noted at all levels of the skin ($P<.0001$), down to 1.8 mm for fluorescence at a clinically relevant dose of 37 J/cm^2. Although this technique may be too invasive for the clinical indication of photorejuvenation, it could have far-reaching implications in the treatment of nonmelanoma skin cancers as well as scar tissue.

In a split-face pilot study of 4 participants using nonablative fractional laser treatment prior to MAL incubation for 3 hours and subsequent treatment with red light, the side of the face treated with MAL showed greater improvement in wrinkles than the untreated side.[37]

Methods for enhancement of PDT results are just beginning to be understood but hold great promise for the potential development of therapies that require fewer treatments to reach greater clinical efficacy as well as therapies that utilize broadband light instead of IPL, as it is less expensive and easier to apply.

CONCLUSION

Photodynamic therapy has many uses in cosmetic dermatology, including reduction of photodamage, mild wrinkles, and enlarged pores; treatment of acne and SGH; and prevention of AKs and nonmelanoma skin cancers. Strategies to enhance the outcome of PDT include increasing photosensitizer absorption via pretreatment with topical therapies; microneedle-assisted infusion prior to application of photosensitizers; and the use of lasers, IR, and other heating modalities to increase conversion of the

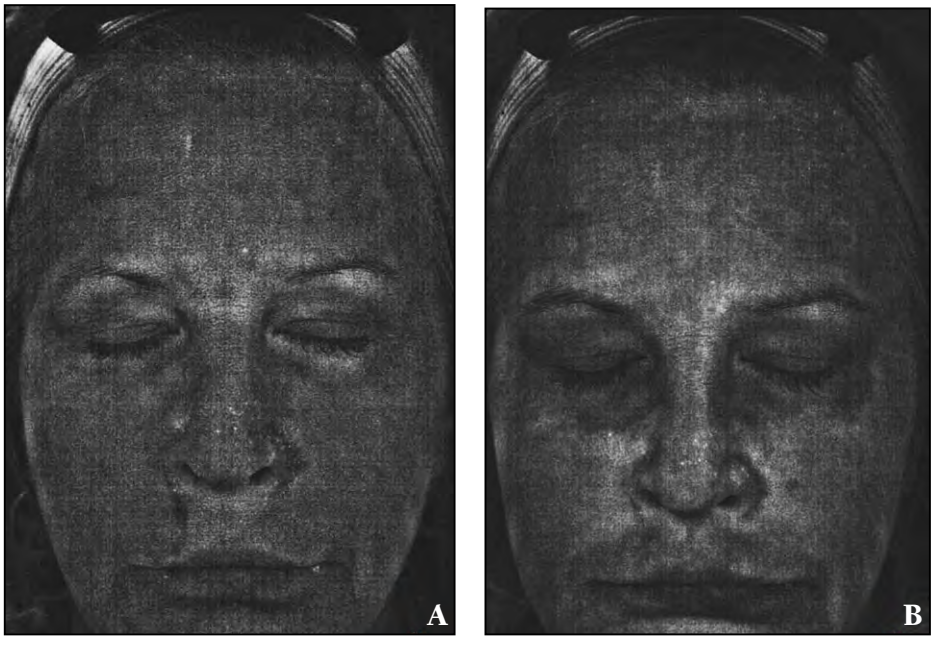

Figure 3. UV photography showing porphyrins only. Immediately after microneedling and application of aminolevulinic acid, almost no porphyrins were present (A). More marked confluent porphyrins (indicated by the lighter areas that are fluorescing) were present within 1 hour of incubation after microneedling and application of aminolevulinic acid (B).

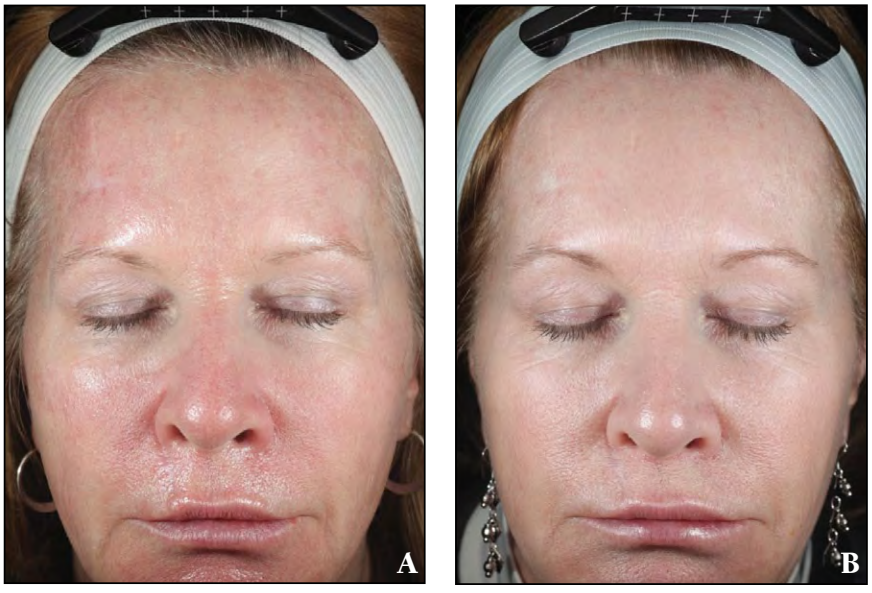

Figure 4. A patient before (A) and 12 days after photodynamic therapy utilizing microneedle-assisted dermal infusion application of aminolevulinic acid 20% and 60-minute incubation followed by blue light for 16 minutes and 40 seconds (B).

prodrug to chromophores. There are many choices of light sources, photosensitizing drugs, and protocols to choose from to achieve excellent results. Photodynamic therapy should be an integral part of every aesthetic practice.

REFERENCES

1. Willey A, Mehta S, Lee PK. Reduction in the incidence of squamous cell carcinoma in solid organ transplant recipients treated with cyclic photodynamic therapy [published online ahead of print November 4, 2009]. *Dermatol Surg.* 2010;36:652-658.
2. Ruiz-Rodriguez R, Sanz-Sánchez T, Córdoba S. Photodynamic photorejuvenation. *Dermatol Surg.* 2002:28;742-744; discussion 744.
3. Alster TS, Tanzi EL, Welsh EC. Photorejuvenation of facial skin with topical 20% 5-aminolevulinic acid and intense pulsed light treatment: a split-face comparison study. *J Drugs Dermatol.* 2005;4:35-38.
4. Gold MH, Bradshaw VL, Boring MM, et al. Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. *Dermatol Surg.* 2006;32:795-801; discussion 801-803.
5. Choi JY, Park GT, Na EY, et al. Molecular changes following topical photodynamic therapy using methyl aminolaevulinate in mouse skin [published online ahead of print April 4, 2010]. *J Dermatol Sci.* 2010;58:198-203.
6. Marmur ES, Phelps R, Goldberg DJ. Ultrastructural changes seen after ALA-IPL photorejuvenation: a pilot study. *J Cosmet Laser Ther.* 2005;7:21-24.
7. Alexiades-Armenakas M. Long-pulsed dye laser-mediated photodynamic therapy combined with topical therapy for mild to severe comedonal, inflammatory, or cystic acne. *J Drugs Dermatol.* 2006;5:45-55.
8. Gold MH, Bradshaw VL, Boring MM, et al. The use of a novel intense pulsed light and heat source and ALA-PDT in the treatment of moderate to severe inflammatory acne vulgaris. *J Drugs Dermatol.* 2004;3(suppl 6):S15-S19.
9. Taub AF. A comparison of intense pulsed light, combination radiofrequency and intense pulsed light, and blue light in photodynamic therapy for acne vulgaris. *J Drugs Dermatol.* 2007;6:1010-1016.
10. Barolet D, Boucher A. Radiant near infrared light emitting diode exposure as skin preparation to enhance photodynamic therapy inflammatory type acne treatment outcome. *Lasers Surg Med.* 2010;42:171-178.
11. Bader RS, Scarborough DA. Surgical pearl: intralesional electrodessiccation of sebaceous hyperplasia. *J Am Acad Dermatol.* 2000;42 (1, pt 1):127-128.
12. Alster TS, Tanzi EL. Photodynamic therapy with topical aminolevulinic acid and pulsed dye laser irradiation for sebaceous hyperplasia. *J Drugs Dermatol.* 2003;2:501-504.
13. Richey DF. Aminolevulinic acid photodynamic therapy for sebaceous gland hyperplasia. *Dermatol Clin.* 2007;25:59-65.
14. Kim S, Cho KH. Clinical trial of pin-point photodynamic therapy using an optic fiber for the improvement of enlarged facial pores: a case study. *J Dermatolog Treat.* 2009;20:36-41.
15. Kim B, Choi J, Park K, et al. Sebum, acne, skin elasticity, and gender difference - which is the major influencing factor for facial pores? [published online ahead of print December 28, 2011]. *Skin Res Technol.* doi:10.1111/j.1600-0846.2011.00605.x.
16. Hongcharu W, Taylor CR, Chang Y, et al. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *J Invest Dermatol.* 2000;115:183-192.
17. Ehrenberg B, Jori G, Moan J, eds. *Photochemotherapy: Photodynamic Therapy and Other Modalities (Proceedings Volume).* Vol 2625. Barcelona, Spain: SPIE Press; 1996.
18. Liebmann J, Born M, Kolb-Bachofen V. Blue-light irradiation regulates proliferation and differentiation in human skin cells. *J Invest Dermatol.* 2010;130:259-269.
19. Choi MS, Yun SJ, Beom HJ, et al. Comparative study of the bactericidal effects of 5-aminolevulinic acid with blue and red light on *Propionibacterium acnes* [published online ahead of print November 3, 2010]. *J Dermatol.* 2011;38:661-666.
20. Shnitkind E, Yaping E, Geen S, et al. Anti-inflammatory properties of narrow-band blue light. *J Drugs Dermatol.* 2006;5:605-610.
21. Trelles MA, Allones I. Red light-emitting diode (LED) therapy accelerates wound healing post-blepharoplasty and periocular laser ablative resurfacing. *J Cosmet Laser Ther.* 2006;8:39-42.
22. Palm MD, Goldman MP. Safety and efficacy comparison of blue versus red light sources for photodynamic therapy using methyl

aminolevulinate in photodamaged skin. *J Drugs Dermatol.* 2011;10:53-60.
23. Sadick NS, Alexiades-Armenakas M, Bitter P Jr, et al. Enhanced full-face skin rejuvenation using synchronous intense pulsed optical and conducted bipolar radiofrequency energy (ELOS): introducing selective radiophotothermolysis. *J Drugs Dermatol.* 2005;4:181-186.
24. Sanclemente G, Medina L, Villa JF, et al. A prospective split-face double-blind randomized placebo-controlled trial to assess the efficacy of methyl aminolevulinate + red-light in patients with facial photodamage. *J Eur Acad Dermatol Venereol.* 2011;25:49-58.
25. Ruiz-Rodríguez R, López L, Candelas D, et al. Photorejuvenation using topical 5-methyl aminolevulinate and red light. *J Drugs Dermatol.* 2008;7:633-637.
26. Touma D, Yaar M, Whitehead S, et al. A trial of short incubation, broad-area photodynamic therapy for facial actinic keratoses and diffuse photodamage. *Arch Dermatol.* 2004;140:33-40.
27. Taub AF. Photodynamic therapy for the treatment of acne: a pilot study. *J Drugs Dermatol.* 2004;3(suppl 6):S10-S14.
28. Warren CB, Lohser S, Wene LC, et al. Noninvasive fluorescence monitoring of protoporphyrin IX production and clinical outcomes in actinic keratoses following short-contact application of 5-aminolevulinate. *J Biomed Opt.* 2010;15:051607.
29. Hwa C, Bauer EA, Cohen DE. Skin biology. *Dermatol Ther.* 2011;24:464-470.
30. Galitzer BI. Effect of retinoid pretreatment on outcomes of patients treated by photodynamic therapy for actinic keratosis of the hand and forearm. *J Drugs Dermatol.* 2011;10:1124-1132.
31. Martin G. Prospective, case-based assessment of sequential therapy with topical Fluorouracil cream 0.5% and ALA-PDT for the treatment of actinic keratosis. *J Drugs Dermatol.* 2011;10:372-378.
32. Katz BE, Truong S, Maiwald DC, et al. Efficacy of microdermabrasion preceding ALA application in reducing the incubation time of ALA in laser PDT. *J Drugs Dermatol.* 2007;6:140-142.
33. Yang J, Chen AC, Wu Q, et al. The influence of temperature on 5-aminolevulinic acid-based photodynamic reaction in keratinocytes in vitro. *Photodermatol Photoimmunol Photomed.* 2010;26:83-88.
34. Clementoni MT, B-Roscher M, Munavalli GS. Photodynamic photorejuvenation of the face with a combination of microneedling, red light, and broadband pulsed light. *Lasers Surg Med.* 2010;42:150-159.
35. Mikolajewska P, Donnelly RF, Garland MJ, et al. Microneedle pretreatment of human skin improves 5-aminolevulininc acid (ALA)- and 5-aminolevulinic acid methyl ester (MAL)-induced PpIX production for topical photodynamic therapy without increase in pain or erythema [published online ahead of print July 31, 2010]. *Pharm Res.* 2010;27:2213-2220.
36. Haedersdal M, Katsnelson J, Sakamoto FH, et al. Enhanced uptake and photoactivation of topical methyl aminolevulinate after fractional CO_2 laser pretreatment. *Lasers Surg Med.* 2011;43:804-813.
37. Ruiz-Rodriguez R, López L, Candelas D, et al. Enhanced efficacy of photodynamic therapy after fractional resurfacing: fractional photodynamic rejuvenation. *J Drugs Dermatol.* 2007;6:818-820.