What's New in Photodynamic Therapy for Photorejuvenation?

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Premature skin aging occurs when exposure to UV light disrupts the balance between normal collagen formation and degradation. Various invasive modalities exist for the treatment of premature skin aging; however, photodynamic therapy (PDT) has emerged as an efficacious treatment option for patients seeking a more noninvasive means to repair photodamaged skin. Photodynamic therapy, a process whereby a photosensitizer and light source in the presence of molecular oxygen selectively destroy a targeted cell, has been explored in combination with various light sources. Treatment paradigms for the off-label use of PDT for photodamage (ie, fine or coarse lines, skin roughness, telangiectases, sallowness) have been established. Recently, the generalizability of PDT has started to change, as the idea of creating safe and effective protocols in darker skin types has just begun to be broached. The minimal side effects and radically reduced incubation times associated with the procedure have made PDT an attractive option for the cosmetic patient. *Cosmet Dermatol.* 2011;24:372-379.

Photoaging is a chemical reaction that occurs when skin is exposed to UV light. Premature skin aging occurs when this reaction disrupts the balance between normal collagen production and degradation. For example, within minutes of UV exposure to the skin, epidermal growth factor, IL-1, and tumor necrosis factor α receptors activate and produce proteolytic enzymes responsible for degrading collagen. Degraded collagen accumulates in the dermis from UV radiation, which antagonizes neocollagenesis.[1]

Histologically, abnormal elastic fibers accumulate in the papillary dermis of sun-damaged skin. Compared to naturally aged, sun-protected skin, photoaged skin has a thicker, rougher, and coarser clinical appearance with mottled pigmentation.[2] Lentigines and diffuse irreversible hyperpigmentation often appear as secondary effects of UV-induced hyperplasia of melanocytes. Additionally, alterations in cutaneous microvasculature, such as regression of small blood vessels and neoangiogenesis, result in telangiectases.[3]

The substantial adverse effects and downtime associated with ablative laser resurfacing techniques have created a niche for alternative skin rejuvenation modalities. Photodynamic therapy (PDT) has emerged as an efficacious treatment for those patients seeking a more noninvasive means to repair photodamaged skin. First used systemically, PDT was discovered as a treatment of internal malignancies when the associated agents were shown to preferentially accumulate and destroy tumor cells of the bladder and esophagus.[4] However, prolonged cutaneous photosensitivity following treatment limited the systemic use of this procedure. In the late 1990s, case reports citing utilization of 5-aminolevulinic acid (ALA) as a topical formulation showed few residual phototoxic effects,[5] and in

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1999, the US Food and Drug Administration approved this agent in combination with light (ALA-PDT) for the treatment of actinic keratoses.[4] Since then, PDT has been studied off label for aesthetic and cosmetic applications. This article will review the mechanism of action of PDT and its molecular effects on photodamaged skin as well as the latest clinical trial literature (2006–present) in which various light and laser sources have been successfully employed for the off-label indication of photorejuvenation.

MECHANISM OF ACTION

Photodynamic therapy is a process whereby a photosensitizer and light source, in the presence of molecular oxygen, selectively destroy a targeted cell. In the United States, ALA and methyl aminolevulinate (MAL) are available for use as photosensitizers. They are metabolized to protoporphyrin IX (PpIX) when applied topically, and free radicals are produced when PpIX is irradiated with visible light, causing injury to various metabolically active cutaneous targets, such as pilosebaceous units or hyperproliferative keratinocytes.[6,7] An esterified derivative of ALA, MAL is considered to be more lipophilic than ALA and has an increased penetration of and higher specificity for PpIX induction in hyperplastic lesions, including precancerous cells. In addition, there is evidence that MAL may provoke less pain during PDT than ALA.[8-10]

The absorption spectrum of PpIX enables the availability of a wide range of electromagnetic radiation options in the visible spectrum. The major absorption peak for ALA, known as the Soret band, is best activated by narrowband blue-light lamps that have an associated 410- to 420-nm wavelength range.[11] However, several other small absorption peaks, known as Q-bands, can be manipulated through the use of a variety of lasers and light sources, such as pulsed dye lasers (PDLs), intense pulsed light (IPL) sources, and red-light sources.[12,13] The deeper-penetrating wavelengths associated with PDL and IPL have an added photothermal effect of reaching thermal target chromophores such as vessels, pigment, and collagen to enhance the cosmetic possibilities.[14]

MOLECULAR EFFECTS OF PDT ON PHOTOAGING

Few studies have quantitatively examined the cellular and molecular changes that occur in the epidermis and dermis after PDT in photodamaged skin. Utilizing a 3-hour application of ALA followed by PDL therapy to focal areas of photodamaged forearms, Orringer et al[15] showed that ALA-PDT enhances dermal remodeling, even after just 1 treatment cycle. Immunohistochemical analysis of serial biopsy specimens taken at baseline and at various times after treatment revealed that epidermal proliferation was stimulated (more than a 5-fold increase, $P<.05$), epidermal thickness was increased (more than a 1.4-fold increase, $P<.05$), and upregulation of collagen was produced (more than a 2.65-fold increase of procollagen I messenger RNA, $P<.05$; more than a 3.32-fold increase of procollagen III messenger RNA, $P<.05$).[15]

These findings of increased collagen production are in keeping with the results of a pilot study by Marmur et al[16] that examined via electron microscopy the ultrastructural changes produced by ALA applications followed by exposure to a noncoherent IPL source. The authors reported that changes in epidermal thickness and collagen upregulation were qualitatively similar to those described in response to topical tretinoin therapy.[16] Therefore, ALA-IPL may provide retinoid-like benefits to the appearance of the skin, with these changes likely occurring more rapidly than with topical retinoid therapy.[17-19]

It should be noted that immunostaining for p53, a marker of photodamage, did not show a decrease following ALA-PDT treatment in the Orringer et al[15] study. Additionally, this study's 3-hour incubation time is substantially longer than the 60-minute incubation period that is generally utilized. Also, the photodamaged skin of the forearm may have varying wound-healing properties in comparison to the face where PDT procedures typically are conducted.[15]

PDT WITH IPL SOURCES

Intense pulsed light has a broad spectrum of wavelength activation (515–1200 nm), which has been shown to independently improve telangiectases and irregular pigmentation. It also is effective as an adjunct to PDT by precisely targeting the Q-bands of PpIX to initiate the photooxidative reaction.[20] Intense pulsed light affords a deeper penetration into the red and near-infrared range, allowing for photothermal activation of various chromophores that further improve skin texture, diminish pigmentation, and decrease overall redness and telangectases.[13,21]

When PDT was initially approved by the US Food and Drug Administration for the treatment of actinic keratoses, ALA solution was applied to the skin 14 to 18 hours before irradiation with a light source. Phase 2 trials showed an 88% clearance of actinic keratoses when 2 long incubation treatments were administered, and more than 94% of trial participants also noted an improvement in skin texture after treatment; however, drawbacks such as stinging and burning during therapy and itching, erythema, and edema after therapy made this treatment regimen unattractive to the majority of dermatologists.[22,23]

In response, several groups began to investigate the use of shorter incubation times with ALA-PDT, and a 1-, 2-, or 3-hour incubation period was discovered to be just as efficacious in clearing actinic keratosis as the initial 14 to 18 hours of incubation.[24] Similar results were reported regarding the effectiveness of the abbreviated incubation time and photorejuvenation.[25] The first split-face clinical study using 3 treatments at 1-month intervals of short-contact ALA-PDT with IPL versus IPL alone was conducted by Gold et al[26] in 2006. The percentage of improvement in the combined treatment side was greater than the control for all facets of photodamage (eg, crow's-feet, tactile skin roughness, mottled hyperpigmentation, telangiectases); however, the authors failed to report if this difference was statistically significant.[26]

More recently, there have been 2 major studies investigating the use of PDT with IPL for photorejuvenation in Asians with Fitzpatrick skin types III and IV (Table). Current ablative photorejuvenation options carry such substantial side-effect profiles (eg, postinflammatory hyperpigmentation and prolonged downtime) that utilization in this patient population is limited.[35] A split-face study of 24 participants comparing ALA-IPL to IPL alone showed that the global photodamage score (50% vs 13%; $P=.005$), fine lines (71% vs 33%; $P=.009$), and coarse wrinkles (50% vs 13%; $P=.005$) were significantly better on the combined treatment side.[27] For safety, ALA solution 5% was used in this study in contrast to the 20% solution that is most often utilized in clinical trials. The IPL energy fluences used were close to half of those used in studies conducted on white participants. Even though satisfactory results were obtained, postinflammatory hyperpigmentation did occur in 2 participants, which was reported to take months to resolve, even with an intensive regimen of oral vitamin C, vitamin E, and topical Centella triterpenes cream used twice daily.[27]

A Japanese group attempted a similar study in 16 participants with Fitzpatrick skin types III and IV utilizing energy fluences that were comparable to those in studies on skin types I and II.[28] Comparative analysis of photorejuvenation showed noticeable improvements on both sides of the face (ALA-IPL vs IPL alone). Although the final scores in the combined treatment side were lower than the control, this difference was not statistically significant. Additionally, all participants in the combined treatment side experienced side effects including mild to severe symptoms of pain, burning sensation, or erythema. Postinflammatory hyperpigmentation was reported in 1 case and was still present at the 3-month follow-up visit.[28] Further studies are required to determine the most favorable protocol, especially in patients with darker skin types.

PDT WITH BLUE OR RED LIGHT

The absorption spectra of porphyrins determine the amount of energy required for a given wavelength to induce an effect. As a result, the absorption maximum of PpIX around 410 nm makes blue light 40 times more potent than red light, which uses smaller absorption peaks at 630 nm.[36] However, at shorter wavelengths, substantial tissue and melanin absorption provide less light penetration, resulting in a blue-light penetration depth of 1 to 2 mm versus a penetration depth of up to 4 mm with red light.[37]

There have been multiple studies to support the photorejuvenation effects of MAL combined with red-light illumination.[29,31] One histopathologic study showed a statistically significant increase in collagen fibers 6 months after treatment with MAL–red light PDT ($P=.008$).[1] Another clinical trial using high-resolution echography showed an increase in skin thickness and reduction of the subepidermal low-echogenic band thickness, suggesting that MAL–red light PDT reshapes and possibly deposits new collagen fibers after only 2 treatments.[32] Most often, ALA-PDT is conducted with blue light, while the use of MAL in Europe historically has been paired with red light. Recently, a split-face trial was conducted in 18 participants who were randomized to treatment with either MAL–red light or MAL–blue light after microdermabrasion and illumination with PDL and IPL.[34] Overall, MAL-PDT was found to be equally effective using red light versus blue light with no differences in categorical photodamage measures, including wrinkles, pigmentation, erythema, or clearance of actinic keratoses. Only 2 participants reported mild discomfort with red-light illumination; no participants experienced discomfort resulting from blue-light exposure.[34]

This study utilized multiple illumination devices, making it difficult to compare red LED to blue light in a head-to-head comparison. The blue light source (417 nm) targeted the Soret band, while the red LED and PDL took advantage of the porphyrin peaks at 630 nm and 690 nm, respectively.[34] The broadband IPL is likely to target numerous peaks along the PpIX spectra.[6,25] The authors speculated that activating the photochemical reactions along multiple peaks of the porphyrin curve may increase the effectiveness of MAL-PDT and lead to superior clinical results.[34] Additionally, PDL targets the chromophore hemoglobin within vessels, thereby reducing erythema.[38] Also, via selective photothermolysis, IPL targets both melanin and vessels, leading to improvement in pigmentation, erythema, and telangiectases. Lastly, combining IPL and PDL can lead to synergistic dermal changes, likely due to fibroblast stimulation and subsequent collagen synthesis.[34]

Outcome of Controlled Studies Using PDT for the Treatment of Photoaging

Reference (Year)	Light Source (Parameters)	Photosensitizer (Incubation Time)	Split Face	Participants, n/ Treatments, n	Treatment Area (Fitzpatrick Skin Type)	Follow-up Period	Results	Side Effects
Xi et al[27] (2010)	IPL (520 nm, 17–20 J/cm^2)	ALA (1 h)	Yes (ALA-IPL vs IPL alone)	24/3	Face (types III and IV)	1 mo	Combination treatment showed significant improvement in global photodamage score (P=.005), fine lines (P=.009), and coarse wrinkles (P=.005)	Moderate erythema, prolonged erythema, edema, and PIH (more intense in the combined treatment side)
Kosaka et al[28] (2010)	IPL (500–670 nm and 870–1400 nm, 23–30 J/cm^2)	ALA (2 h)	Yes (ALA-IPL vs IPL alone)	16/3	Face (types III and IV)	3 mo	Noticeable improvements on both sides of face; reduction in the photoaging score did not significantly differ	Mild to severe pain, burning sensation, or erythema in all ALA-IPL participants
Gold et al[26] (2006)	IPL (550 nm, 34 J/cm^2)	ALA (1 h)	Yes (ALA-IPL vs IPL alone)	13/3	Face (types I–IV)	3 mo	Combined treatment showed more improvement for crow's-feet, tactile skin roughness, mottled hyperpigmentation, and telangiectases	Erythema and edema on both sides of the face

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Reference (Year)	Light Source (Parameters)	Photosensitizer (Incubation Time)	Split Face	Participants, n/ Treatments, n	Treatment Area (Fitzpatrick Skin Type)	Follow-up Period	Results	Side Effects
Sanclemente et al[29] (2011)	Red light (635 nm, 37 J/cm^2)	MAL (3 h)	Yes (MAL–red light vs placebo–red light)	48/2	Face (N/A)	1 mo	Combined treatment showed significant improvement (P=.0000) in global photodamage, fine lines, coarse lines, mottled pigmentation, tactile roughness, and sallowness	Combined treatment showed significantly (P=.0000) more pain, erythema, edema, desquamation, and vesiculation
Clementoni et al[30] (2010)	Microneedling pretreatment + broadband pulsed light (560 nm, 19–22 J/cm^2) + red light (630 nm, 75 J/cm^2)	ALA (1 h)	No	21/1	Face (types II and III)	6 mo	Significant improvement (P<.05) in global photodamage, fine lines, mottled pigmentation, sallowness, tactile roughness, and telangiectases	All participants had fine desquamation that terminated by 7 d posttreatment
Issa et al[1] (2010)	Red light (635 nm, 37 J/cm^2)	MAL (2 h)	No	14/2	Face (type III)	6 mo	Improvement in texture, firmness, wrinkle depth, and skin coloration; statistically significant (P=.008) increase in collagen fibers	Majority of adverse effects were classified as mild
Ruiz-Rodríguez et al[31] (2008)	Red light (635 nm, 37 J/cm^2)	MAL (1 h vs 3 h)	Yes (1 h vs 3 h incubation)	10/3	Face (types II and III)	2 mo	3 h: moderate improvement of skin tightness, fine wrinkles, and tactile roughness	3 h: erythema and edema, scaling

Reference (Year)	Light Source (Parameters)	Photosensitizer (Incubation Time)	Split Face	Participants, n/ Treatments, n	Treatment Area (Fitzpatrick Skin Type)	Follow-up Period	Results	Side Effects
Zane et al[32] (2007)	Red light (635 nm, 37 J/cm^2)	MAL (3 h)	No	20/2	Face (types II and III)	2 mo	Significant improvement ($P<.05$) of mottled hyperpigmentation, fine lines, roughness, and sallowness	Erythema, edema, crusting, and erosions
Ruiz-Rodriguez et al[33] (2007)	Red light (635 nm, 37 J/cm^2) + fractional resurfacing	ALA (3 h)	Yes (ALA–red light + fractional resurfacing vs fractional resurfacing alone)	4/2	Perioral (types II and III)	4 mo	Combined treatment showed increased improvement in wrinkles	Combined treatment showed increased erythema, edema, and scaling
Palm et al[34] (2011)	Microdermabrasion + PDL (690 nm, 10–12 J/cm^2) +/− IPL (520 nm, 17−20 J/cm^2) + either red light (630 nm, 37 J/cm^2) or blue light (417 nm, 10 J/cm^2)	MAL (1 h)	Yes (MAL–blue light vs MAL–red light)	18/1	Head and neck (types I–III)	1 mo	No statistically significant differences in signs of photodamage of MAL-PDT with blue light vs red light	Mild erythema resolved by day 7
Orringer et al[15] (2008)	PDL (595 nm, 7.5 J/cm^2)	ALA (3 h)	No	25/1	Forearms (N/A)	6 mo	Stimulation of epidermal proliferation, epidermal injury produced, and upregulation of collagen	None reported

Abbreviations: PDT, photodynamic therapy; IPL, intense pulsed light; ALA, 5-aminolevulinic acid; PIH, postinflammatory hyperpigmentation; MAL, methyl aminolevulinate; N/A not available; PDL, pulsed dye laser.

Multiple illumination devices also were used in an ALA-PDT trial involving 21 participants; microneedling was followed by red light and broadband pulsed light.[30] Microneedle rollers boost cosmesis through collagen induction and increase penetration of topical cosmeceuticals. The roller, which is embedded with stainless steel, solid-bore needles that are 108 µm in width and 300 µm in length, creates numerous transdermal channels to augment topical penetration of ALA. Statistically significant improvement was seen in the global photoaging scores at 3 months compared to baseline ($P<.05$); however, a lack of appropriate controls in this pilot study inhibits extrapolation of the results reported.[30]

The combination of an ablative device with PDT has been explored by Ruiz-Rodriguez et al[33] who treated half of the perioral area in 4 women with fractional resurfacing and ALA–red light PDT in 2 treatment sessions that were 3 weeks apart. Compared to fractional resurfacing alone, the combination treatment showed an increased improvement in superficial wrinkles in 3 participants. Although the power of this pilot study is low, the results affirm that clinical cosmetic results can be synergistically advanced by combining ablative methodologies with PDT.[33]

CONCLUSION

The technological evolution of PDT has made the procedure a powerful utility for patients seeking noninvasive methods to photorejuvenate the skin. Manipulation of the PpIX absorption spectra with different illumination devices, combination with ablative techniques, and pretreatment of the skin with microdermabrasion or microneedling have augmented the cosmetic efficacy of PDT. The generalizability of PDT also has begun to change, as the idea of creating safe and effective protocols in patients with darker skin types has just begun to be broached. The minimal side effects and radically reduced incubation times associated with this procedure have made PDT an attractive option for the cosmetic patient.

REFERENCES

1. Issa MC, Piñerio-Maceira J, Vieira MT, et al. Photorejuvenation with topical methyl aminolevulinate and red light: a randomized, prospective, clinical, histopathologic, and morphometric study [published online ahead of print December 4, 2009]. *Dermatol Surg.* 2010;36:39-48.
2. Park MY, Sohn S, Lee ES, et al. Photorejuvenation induced by 5-aminolevulinic acid photodynamic therapy in patients with actinic keratosis: a histologic analysis [published online ahead of print November 18, 2009]. *J Am Acad Dermatol.* 2010; 62:85-95.
3. Plewig G, Kligman AM. Proliferative activity of the sebaceous glands of the aged. *J Invest Dermatol.* 1978;70:314-317.
4. Goldberg DJ. Photodynamic therapy in skin rejuvenation. *Clin Dermatol.* 2008;26:608-613.
5. Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. *J Photochem Photobiol B.* 1990;6:143-148.
6. Uebelhoer NS, Dover JS. Photodynamic therapy for cosmetic applications. *Dermatol Ther.* 2005;18:242-252.
7. Dolmans DE, Fukumura D, Jain RK. Photodynamic therapy for cancer. *Nat Rev Cancer.* 2003;3:380-387.
8. Pariser DM, Lowe NJ, Stewart DM, et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. *J Am Acad Dermatol.* 2003;48:227-232.
9. Wiegell SR, Stender IM, Na R, et al. Pain associated with photodynamic therapy using 5-aminolevulinic acid or 5-aminolevulinic acid methylester on tape-stripped normal skin. *Arch Dermatol.* 2003;139:1173-1177.
10. Kasche A, Luderschmidt S, Ring J, et al. Photodynamic therapy induces less pain in patients treated with methyl aminolevulinate compared to aminolevulinic acid. *J Drugs Dermatol.* 2006;5: 353-356.
11. Gold MH. Therapeutic and aesthetic uses of photodynamic therapy part five of a five-part series: ALA-PDT and MAL-PDT what makes them different. *J Clin Aesthet Dermatol.* 2009;2:44-47.
12. Nestor MS, Gold MH, Kauvar AN, et al. The use of photodynamic therapy in dermatology: results of a consensus conference. *J Drugs Dermatol.* 2006;5:140-154.
13. Szeimies RM, Abels C, Fritsch C, et al. Wavelength dependency of photodynamic effects after sensitization with 5-aminolevulinic acid in vitro and in vivo. *J Invest Dermatol.* 1995;105: 672-677.
14. Goldberg D, Tan M, Dale Sarradet M, et al. Nonablative dermal remodeling with 585-nm, 350-microsec, flashlamp pulsed dye laser: clinical and ultrastructural analysis. *Dermatol Surg.* 2003;29:161-163; discussion 163-164.
15. Orringer JS, Hammerberg C, Hamilton T, et al. Molecular effects of photodynamic therapy for photoaging. *Arch Dermatol.* 2008;144:1296-1302.
16. Marmur ES, Phelps R, Goldberg DJ. Ultrastructural changes seen after ALA-IPL photorejuvenation: a pilot study. *J Cosmet Laser Ther.* 2005;7:21-24.
17. Griffiths CE, Russman AN, Majmudar G, et al. Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). *N Engl J Med.* 1993;329:530-535.
18. Rittié L, Varani J, Kang S, et al. Retinoid-induced epidermal hyperplasia is mediated by epidermal growth factor receptor activation via specific induction of its ligands heparin-binding EGF and amphiregulin in human skin in vivo. *J Invest Dermatol.* 2006;126:732-739.
19. Kang S, Voorhees JJ. Photoaging therapy with topical tretinoin: an evidence-based analysis. *J Am Acad Dermatol.* 1998;39 (2, pt 3):S55-S61.
20. Jorgensen GF, Hedelund L, Haedersdal M. Long-pulsed dye laser versus intense pulsed light for photodamaged skin: a randomized split-face trial with blinded response evaluation. *Lasers Surg Med.* 2008;40:293-299.
21. Bitter PH. Noninvasive rejuvenation of photodamaged skin using serial, full-face intense pulsed light treatments. *Dermatol Surg.* 2000;26:835-842; discussion 843.
22. Jeffes EW, McCullough JL, Weinstein GD, et al. Photodynamic therapy of actinic keratoses with topical aminolevulinic acid hydrochloride and fluorescent blue light. *J Am Acad Dermatol.* 2001;45:96-104.

23. Jeffes EW. Levulan: the first approved topical photosensitizer for the treatment of actinic keratosis. *J Dermatolog Treat.* 2002;13 (suppl 1):S19-S23.
24. 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.
25. Avram DK, Goldman MP. Effectiveness and safety of ALA-IPL in treating actinic keratoses and photodamage. *J Drugs Dermatol.* 2004;3(suppl 1):S36-S39.
26. 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.
27. Xi Z, Shuxian Y, Zhong L, et al. Topical 5-aminolevulinic acid with intense pulsed light versus intense pulsed light for photodamage in Chinese patients [published online ahead of print September 17, 2010]. *Dermatol Surg.* 2011;37:31-40.
28. Kosaka S, Yasumoto M, Akilov OE, et al. Comparative split-face study of 5-aminolevulinic acid photodynamic therapy with intense pulsed light for photorejuvenation of Asian skin [published online ahead of print August 16, 2010]. *J Dermatol.* 2010;37: 1005-1010.
29. 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.
30. 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.
31. Ruiz-Rodríguez R, López L, Candelas D, et al. Photorejuvenation using topical 5-methyl aminolevulinate and red light. *J Drug Dermatol.* 2008;7:633-637.
32. Zane C, Capezzera R, Sala R, et al. Clinical and echographic analysis of photodynamic therapy using methylaminolevulinate as sensitizer in the treatment of photodamaged facial skin. *Lasers Surg Med.* 2007;39:203-209.
33. 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.
34. 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.
35. Chan HH, Manstein D, Yu CS, et al. The prevalence and risk factors of postinflammatory hyperpigmentation after fractional resurfacing in Asians. *Lasers Surg Med.* 2007;39:381-385.
36. Kohl E, Torezan LA, Landthaler M, et al. Aesthetic effects of topical photodynamic therapy. *J Eur Acad Dermatol Venereol.* 2010;24:1261-1269.
37. Morton CA, McKenna KE, Rhodes LE; British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update [published online ahead of print October 13, 2008]. *Br J Dermatol.* 2008;159:1245-1266.
38. DeHoratius DM, Dover JS. Nonablative tissue remodeling and photorejuvenation. *Clin Dermatol.* 2007;25:474-479.