Photodynamic therapy for acne, a work in progress

By Jan Bowers, contributing writer, March 01, 2011

One of several light-based technologies under investigation for the treatment of acne vulgaris, photodynamic therapy (PDT) has shown impressive long-term results that may approach those achieved by isotretinoin. Defined as the interaction of a photosensitizing agent, a light source, and oxygen, PDT is approved by the U.S. Food and Drug Administration (FDA) only for the treatment of actinic keratosis. Its off-label application in the treatment of acne was first reported in two studies in 2000, and numerous studies investigating different aspects of the treatment have been published since then. While some clinicians have embraced its use, PDT faces a number of challenges to becoming a mainstream acne treatment, in addition to its lack of FDA approval: a lack of consensus around optimal treatment parameters and methodology, and severe side effects resulting in patient compliance issues.

Alternatives to conventional treatment needed

"I feel there's increasing interest in PDT right now because it's getting more difficult to prescribe isotretinoin, and clinicians need an alternative for those patients who don't respond to conventional treatment," says Fernanda H. Sakamoto, MD, instructor in dermatology at Harvard Medical School and a researcher at the Wellman Center for Photomedicine, referring to the hurdles the iPledge program creates for patients and isotretinoin's side effects, which may give patients pause. Dr. Sakamoto and co-authors Jose Daniel Lopes, MD, PhD, R. Rox Anderson, MD, and Luis Torezan, MD, published a comprehensive, two-part continuing medical education article examining the literature and the state of clinical practice of PDT for acne in the September 2010 issue of the *Journal of the American Academy of Dermatology*. Explaining the need for an alternative to isotretinoin for treating moderate to severe acne, the authors point out that up to half of patients receiving isotretinoin relapse within two years, and that oral isotretinoin poses a high risk of fetal defects when taken before or during pregnancy. In addition, the patient's liver function and serum lipids must be monitored, and side effects can include dry skin and lips, gastrointestinal symptoms, headaches, and mood changes. The side effects of isotretinoin drive some patients to discontinue treatment, while the risks cause other acne sufferers (or their parents) to decline this treatment.

PDT shows efficacy

Noting that bright visible light can moderately improve acne, Drs. Sakamoto, Lopes, and Anderson say it appears that "naturally occurring porphyrins within sebaceous follicles act as endogenous photosensitizers to visible light." Intense blue light is an FDA-approved treatment for acne, but the

authors state that all light-alone treatments have only temporary effects and seem to be effective only against mild to moderate acne.

One of two approved photosensitizers, 5-Aminolevulinic acid (ALA), was observed to induce strong porphyrin fluorescence in sebaceous glands and hair follicles in an early test of the efficacy of PDT, co-authored by Dr. Anderson and published in the August 2000 issue of the *Journal of Investigative Dermatology*. The investigators applied a 20 percent formulation of ALA under occlusion for three hours, then delivered high-dose broadband red light to large sites on the skin of adults with back acne. The ALA-PDT combined therapy was compared with red light alone, ALA alone, and no treatment, and a group receiving only one PDT treatment was compared with another receiving four treatments at one-week intervals. The results, summarized by Drs. Sakamoto, Lopes, and Anderson, showed "statistically significant and obvious improvement of acne assessed blindly" and reduction of sebum output over 20 weeks of patient follow-up in the patients receiving PDT, with the best results observed in the group receiving four PDT treatments.
Though PDT's mechanism of action is not completely understood, the*JAAD* authors suggest a number of ways in which the treatment tested in the 2000 study likely achieved its results. These include: destruction of sebaceous glands, decreasing sebum production, a possible enhancement of epidermal turnover (which in turn would reduce hyperkeratosis and unplug follicles), and a possible down-regulating effect on infiltrating inflammatory cells within acne lesions. They note that investigators in the 2000 study did not observe a reduction in the number of Propionibacterium acnes. More recently however, a review in the September 2010 issue of the *Journal of Cosmetic Dermatology*, co-authored by Mohammed L. Elsaie, MD, and Sonal Choudhary, MD, cited two studies that showed ALA-PDT did reduce the number of P. acnes; the mechanism of action therefore remains uncertain.

Optimal treatment parameters elusive
In addition to choosing between two available photosensitizers (ALA and its derivative, methyl-aminolevulinate [MAL]), clinicians offering PDT to their patients must consider various light sources and wavelengths, light dosimetry, drug incubation time, and skin preparation (see sidebar below). Despite the wealth of published studies examining PDT for acne, none of the variables has been optimized for this treatment, says Dr. Sakamoto. "Because there's no consensus about this right now, there's a lot of debate and people don't agree as to the best way to deliver PDT," she says. "We wrote our review article to try to raise the question and come up with the best we could out of the current literature."

Drs. Choudhary and Elsaie expressed a similar goal in conducting their review for the *Journal of Cosmetic Dermatology*. "There's no consensus, no standardization, no rationales for the PDT treatment of acne," says Dr. Elsaie, an instructor of dermatology at the University of Miami Miller School of Medicine and instructor of dermatology at the National Research Center in Cairo, Egypt. Dr. Choudhary, a clinical research fellow in the department of dermatology and cutaneous surgery at the Miller School of Medicine, says she suspects that "probably very few dermatologists have tried PDT for acne. So a review of this kind may help build awareness of where this modality stands." Drs. Sakamoto, Torezan, and Anderson analyzed 18 clinical studies published through 2009 on the subject of PDT for acne. Drs. Elsaie and Choudhary analyzed 22 studies.
Making sense of the evidence
Looking at the combinations of treatment parameters most frequently studied, Dr. Sakamoto views them in two broad categories: "high-dose" and "low-dose" PDT. These terms refer not only to dosimetry, but also to the wavelength of the light and the length of the incubation period. In this

context, “high-dose” PDT uses high fluence red light after an incubation period of at least three hours and for multiple sessions. “The high-dose treatment seems to be giving a more prolonged result by destroying the glands,” says Dr. Sakamoto. “The low-dose PDT would be any variation with shorter duration, different concentrations, and so on. But with low-dose treatment, there’s not much scientific proof that we are actually destroying the glands; maybe we are treating the acne temporarily.”

While the *JAAD* review authors note several studies that utilized shorter incubation times, lower fluences, and wavelengths other than red, they point out various shortcomings in these studies ranging from suboptimal study design to poor statistical analysis. Despite this, Dr. Sakamoto says she believes “most clinicians who are treating acne with PDT are using low-dose methods” in an effort to make the treatment more easily tolerated and less time-consuming. Drs. Elsaie and Choudhary also state that “multiple treatments appeared to be superior to single treatments, especially at longer follow-up periods.”

Side effects a stumbling block

The most common side effects of PDT for acne are moderate to severe pain, erythema (typically lasting three to five days), edema (usually occurring one to four days after treatment), and hyperpigmentation which can persist up to four weeks after a treatment. Other adverse effects can include sterile pustular eruption, crusts, purpura, and acute transient acne flare. Pain typically begins within a minute of light exposure, peaks within several minutes, subsides as photobleaching of the porphyrin occurs, and ceases when the light is turned off.

rs. Sakamoto, Elsaie, and Choudhary all cite these side effects as a key barrier to broader adoption of this treatment method. “Because the treatment is so painful and because you need to restrict your exposure to sunlight for 48 hours following treatment, patient selection and patient compliance are very challenging issues,” says Dr. Elsaie. “In addition, PDT can require up to six weekly or monthly treatments. For all these reasons, teenagers in particular tend to drop out of treatment.”

While some studies indicate that pain during PDT can be minimized by spritzing the treatment area with cool water and using a fan to blow air across the skin, pain and other side effects are currently an inevitable part of the most effective forms of PDT. “If you want to get a good result, as a patient you have to bear with the side effects,” says Dr. Sakamoto. “As for the clinician, you have to spend a lot of time with the patient during a long incubation, and then patients will likely call you about their side effects, so you have to have a very good support team.”

Future directions

The goal of duplicating the best results of PDT studies while mitigating the adverse effects is driving researchers to tweak various treatment parameters and to investigate other forms of light-based treatment for acne. Researchers at the Wellman Center are focused on optimizing PDT treatment using the current photosensitizers, says Dr. Sakamoto. “We’re changing the techniques of how we do the treatment, playing with many of the variables such as incubation period, application of the drug, and light radiation,” she says. “We’re running some clinical trials right now and anticipate that eventually our research will have an impact on the side effects of PDT.”

At the University of Miami, Drs. Elsaie and Choudhary are preparing a protocol for a Phase 3 study to test a photopneumatic therapy that uses a vacuum-assisted pulsed light device emitting broadband light in the range of 400 to 1200 nm. “The effect is very similar to what PDT would do: causing the reactive oxygen species to target the bacteria

P. acnes," says Dr. Choudhary. "The device does not use a photosensitizer, and therefore it is reported to be painless. The first patient we treated, a year ago, is still coming back for follow-up, but not for additional treatment. We have treated several patients, and they're all happy with the results." The device is FDA-approved for treating mild to severe inflammatory acne.

In the meantime, experts agree that PDT may still have a place in the treatment armamentarium. "The role of PDT is a little dicey, but we believe dermatologists should discuss it with patients as a treatment option," says Dr. Choudhary. "There are many people who can't take isotretinoin, so PDT seems to be a great alternative treatment," says Dr. Sakamoto. "It's a trade-off. The way PDT is best performed today, in a high-dose modality, it's not easy on the patient. But in the end, they're very happy with the results."

Key findings

In a pair of articles in the September 2010 issue of the *Journal of the American Academy of Dermatology*, authors Fernanda H. Sakamoto, MD, R. Rox Anderson, MD, Jos Daniel Lopes, MD, PhD, and Luis Torezan, MD, offered a review of the current state of practice of photodynamic therapy as a treatment for acne vulgaris. Some of the key findings:

- Photodynamic therapy for acne vulgaris appears to be safe and effective.
- Blue light by itself can improve acne temporarily due to its anti-inflammatory effects.
- Red light along with photosensitizers has the best long-term results, especially when the light source is continuous and high-intensity.
- Questions remain about the best light dosimetry.
- PDT may be painful for patients, and they may be photosensitive for two days after treatment.

Key PDT parameters

The variables associated with each of the key treatment parameters involved in PDT include:

Photosensitizer — ALA, available in 20 percent hydroalcoholic solution, and MAL, available in a cream formulation of 16 percent, have different mechanisms of cell uptake and transport. New ALA derivatives are in development, but clinical results are not yet available. In studies of acne therapy using a long incubation time and high fluence red light exposure, ALA and MAL have shown similar efficacy. While more comparative studies are needed, they seem largely equivalent.

Light source and wavelength — Continuous wave (CW) and pulsed light sources, including intense pulsed lights (IPLs) and pulsed dye lasers (PDLs), and diode lasers have all been studied in PDT for acne. Light sources tested include light-emitting diodes, filtered incandescent or arc lamps, slide projectors, fluorescent lamps, filtered xenon flashlamps, lasers, and sunlight. Red light (a longer wavelength with deeper penetration) and blue light (a shorter wavelength with the strongest porphyrin absorption) are the most frequently studied in PDT for acne research.

Dosimetry — The primary units of dosimetry are wavelength range of the source, irradiance (the rate at which energy is delivered per unit area of skin) fluence (the total energy delivered per unit area of skin), and exposure time. At the present time there is no consensus on the optimal dosimetry for PDT of acne.

Skin preparation — No clinical comparison of pretreatment care has been reported for PDT using either ALA or MAL. Drs. Sakamoto, Torezan, and Anderson note that skin preparation was not mentioned in several of the studies they analyzed. Among those that did describe preparation, methods included cleansing with 70 percent isopropyl alcohol, mild skin cleansers, 2 percent salicylic acid, and soap and water followed by alcohol scrubbing. Ten of 18 publications recommended occlusion during the drug incubation time, which may increase drug uptake.

Incubation time — The time between drug application and irradiation can range from as few as 10 minutes to three to four hours. While a few studies have suggested shortening the incubation period to 10 to 30 minutes, Drs. Sakamoto, Torezan, and Anderson report that the strongest evidence points to a period of at least three hours.