Lasers and Light Devices for Psoriasis, Part 2: PDL, Nd:YAG Laser, CO_2 Laser, and PDT

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Psoriasis is a common inflammatory skin condition with high morbidity. Lasers are used extensively in dermatology to treat various conditions with proven efficacy and safety and have been investigated as alternatives for treating psoriasis due to side effects that can occur with long-term use of potent topical corticosteroids. Part 1 of this series reviewed the efficacy and safety of the 308-nm excimer laser, psoralen plus UVA, and narrowband UVB (NB-UVB) in the treatment of psoriasis. Part 2 evaluates a range of potential laser and light modalities that are being investigated as treatment options for psoriasis, including the pulsed dye laser (PDL), the 1064- and 1032-nm Nd:YAG lasers, the CO_2 laser, and photodynamic therapy (PDT). Although some of these options have demonstrated inferior clinical and histologic results compared to topical therapies, many patients experience refractory symptoms from psoriasis that could potentially benefit from nontraditional treatment approaches. Future application of these laser and light treatments may be in combination with established topical therapies to prolong remission times and effectively control recalcitrant cases.

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Psoriasis is a prevalent inflammatory skin condition that is characterized by chronic T-cell stimulation, abnormal proliferation of dermal vasculature, and parakeratotic epidermal hyperplasia. Although the clinical presentation of psoriasis may vary, the common manifestation involves well-demarcated plaques with overlying scales affecting the extremities, intertriginous regions, and nails. The presentation of psoriasis can elicit notable patient discomfort, and many treatment modalities continue to be pursued in an effort to adequately address the effects of this disease. We review a range of treatment modalities, including the pulsed dye laser (PDL), Nd:YAG laser (both 1064 and 1320 nm), CO_2 laser, and photodynamic therapy (PDT). Although some of these options have demonstrated inferior clinical and histologic results compared to topical therapies, many patients experience refractory skin and nail disease that may benefit from nontraditional treatment approaches. Future application of these laser and light treatments may be in combination

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with established topical therapies to prolong remission times and effectively control recalcitrant cases.

PULSED DYE LASER

Emitting a wavelength of 585 nm in the yellow light range, the PDL was approved by the US Food and Drug Administration (FDA) in 1986. It was initially evaluated by Hacker and Rasmussen[1] in 1992 for psoriasis. The current recommended settings include a pulse duration of 450 microseconds, a spot size of 5 to 10 mm, and a fluence of at least 8 J/cm^2.[2] The PDL has been successfully utilized for treatment of vascular ectatic lesions such as port-wine stains. Given the abnormal vascularization that occurs early in the disease process, interest developed in the possible application of this laser for the treatment of psoriasis.[3] The altered microvasculature of psoriasis, which precedes epidermal hyperplasia and clinical lesions, can be effectively targeted because oxyhemoglobin avidly absorbs the PDL wavelength.[4]

In a study of 11 patients, Noborio et al[2] demonstrated that there was a positive correlation between microvessel number (via biopsy immunohistology) and plaque severity score; greater clinical improvement was associated with more extensive microvasculature destruction following PDL treatment. The relationship between microvascular density and tortuosity and plaque severity also has been confirmed in vivo by Hern et al.[4]

The efficacy of PDL has been compared to other treatment modalities, including topical agents and other laser and light therapies. One study showed that PDL and calcipotriol/betamethasone dipropionate (CBD) ointment were comparable in efficacy at 4 weeks, but at 8 weeks, PDL was superior based on a reduction in dermal and epidermal T-cell infiltration. At 12 weeks, there also was a significant reduction in epidermal proliferation in plaques treated with PDL compared with CBD ($P<.001$), suggesting a longer remission duration in PDL-treated skin.[5] Another study by Ilknur et al[6] compared the results of treatment with PDL alone, PDL in combination with salicylic acid, and topicals alone (salicylic acid and clobetasol) in 22 patients with chronic stable psoriasis. The findings demonstrated that treatment with topicals alone outperformed both PDL alone and PDL with salicylic acid. Combined treatment with PDL and salicylic acid was superior to PDL alone, measured by psoriasis area and severity index score and plaque surface area.[6] Taibjee et al[7] demonstrated that psoriatic plaques treated with the 308-nm excimer laser showed better clinical improvement than those treated with PDL; however, the authors also noted a subset of patients who responded better to PDL. Pulsed dye laser treatment also has been compared to local narrowband UVB (NB-UVB) therapy. One study found that molecular and cellular changes, such as expression of vascular endothelial growth factor receptors 2 and 3, IL-23, E-selectin, and dermal T-cell infiltrates, all were comparably diminished in both PDL and local NB-UVB treatment groups, with speculation that UVB efficacy was compromised given the local administration, instead of systemic administration, used in this study.[8]

The PDL also has been investigated in treatment of other variants of psoriasis. In one study, 31 of 41 (76%) participants with therapy-resistant psoriasis of the hands and feet demonstrated at least 71% improvement when treated with PDL and a topical agent, either salicylic acid or calcipotriol. The average duration of remission was 10.7 months.[9] Oram et al[10] used a 595-nm PDL in the treatment of nail psoriasis in 5 patients and observed that nail matrix findings, such as subungual hyperkeratosis and onycholysis, responded particularly well to treatment; however, nail pitting persisted in 3 patients after 3 months of treatment.

Nd:YAG LASER

1064 nm

The 1064-nm Nd:YAG laser, FDA approved for dermatologic application in 2000, may be able to target dilated papillary dermal blood vessels, which supply the inflammatory mediators that extravasate into the interstitium. These dermal vessels are located up to a few millimeters deep in the skin. The Nd:YAG laser could theoretically have an advantage in treating psoriasis because of its capability of penetrating the skin up to a depth of 7 mm, thereby facilitating destruction of deeper vessels. The 1064-nm laser has only recently been introduced in the treatment of psoriasis; therefore, the optimal settings are still being determined. In one study, van Lingen et al[11] tested various settings and recommended a 1.5-mm spot size with a fluence of 375 J/cm^2. The study investigated the 1064-nm Nd:YAG laser as a treatment of localized psoriasis in 4 patients and compared results to the well-established CBD topical treatment. Results demonstrated that CBD was more clinically effective than the Nd:YAG laser for treating psoriatic plaques. The Nd:YAG laser resulted in improvement of psoriatic lesion severity scores (SUM score), which is comprised of ratings of erythema, induration, and scaling based on a scale of 0 (absent) to 4 (severe). Note that a total score of 0 represents no psoriasis, and a combined score of 12 indicates the highest possible plaque severity. However, improvement was transient. The reduction in plaques at 4 weeks was not maintained at subsequent 8- and 12-week follow-up. This result was inferior to CBD treatment, which demonstrated improved SUM scores at each interval. Based on immunohistochemical analysis, the Nd:YAG laser

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significantly reduced the number of cells staining positive for $CD3^+$ in the dermis ($P<.05$) but CBD did not; however, CBD treatment significantly decreased $CD3^+$ lymphocytes in the epidermis and the Nd:YAG laser did not ($P<.05$). There also were no side effects following treatment with CBD, but side effects from Nd:YAG therapy included discoloration, crusting of the affected area, fluid leakage from the area, and itching, though no scarring was reported.[11] Although data on this laser are scarce, this modality has shown no known benefit over standard topical therapy, which suggests that targeting the deeper vasculature does not confer enhanced treatment value.

1320 nm

The 1320-nm Nd:YAG laser also has been explored as a possible treatment option for psoriasis, though data are limited. It was FDA approved for dermatologic surgery in 2001. The recommended settings include a pulse duration of 300 to 450 microseconds, a fluence of 6 J/cm^2, and a spot size ranging from 3 to 10 mm.

Ruiz-Esparza[12] observed 3 cases in which treatment of psoriasis with the 1320-nm Nd:YAG laser demonstrated improvement up to 3 months after treatment. Two of 3 (67%) patients demonstrated complete clearance, while the third showed decreased fissuring of palmoplantar lesions. The author hypothesized that the laser had a photochemical effect on dermal fibroblasts that was thought to influence keratinocyte hyperproliferation. An alternative hypothesis proposed that the laser had a direct effect on keratinocyte activity. Although potentially promising, the results of this study are limited given the lack of randomization, limited number of patients, and subjectivity of outcomes[12]; therefore, future investigations using this laser are necessary to evaluate its efficacy.

CO_2 LASER

There are several hypotheses of how the CO_2 laser may be effective for psoriasis. One theory is that the device incites the destruction of the superficial dermal microvasculature that contributes to the pathogenesis of psoriasis; another proposes that the CO_2 laser destroys the fibroblasts in the upper dermis, which are known to induce hyperproliferation of normal keratinocytes.[13,14] Another possible mechanism is that the CO_2 laser severs the cutaneous nerve endings, which are a source of psoriasis-provoking neuropeptides.[14]

In 1986, 3 case reports demonstrated good results following treatment of localized psoriatic plaques with a high-energy CO_2 laser set at a 10,600-nm wavelength on continuous mode with a spot size of 2 mm.[15] These settings were assumed to be efficacious, as this device is known to penetrate the skin to a depth of approximately 1 mm. There was no recurrence of psoriasis after 3.5 years and 2.5 years in 2 patients.[15] The hypothesized mechanism in these cases was that the psoriatic plaque could heal following obliteration of the surface microvessels.[15,16]

A pilot study based on this theory was performed using the pulsed or scanned CO_2 laser on 12 patients with psoriasis.[17] Despite complete ablation of the epidermis and papillary dermis, psoriasis recurred in most patients within 8 weeks; however, 2 patients demonstrated no recurrence after 4 months, both in the group receiving treatment with the pulsed and scanned CO_2 lasers.

PHOTODYNAMIC THERAPY

Photodynamic therapy involves the activation of a photosensitizer by visible light to create cytotoxic oxygen species and free radicals, which selectively destroy rapidly proliferating cells.[18,19] Various light sources are available for PDT, including blue lights, red lights, incoherent lamps, and light-emitting diodes (LEDs).[20] The first stage of PDT includes the administration of a photosensitizer. In the United States, an alcohol-containing 5-aminolevulinic acid (ALA) solution as well as methylaminolevulate are the approved photosensitizers.[21]

After the optimum ratio of the photosensitizer is achieved in the targeted versus healthy cells, a carefully regulated dose of light is shone directly onto the diseased tissue for a specified length of time corresponding with the amount of energy sufficient to activate the photosensitizer. The activation of the photosensitizer evokes photochemical reactions that produce toxic agents, such as the reactive oxygen species, and these radicals result in tissue destruction.[21]

The expressions of transforming growth factor β1 and IL-10, which is an anti-inflammatory cytokine, also may contribute to the improvement observed in patients treated with PDT. For instance, cultured fibroblasts demonstrated reduced transforming growth factor β1 messenger RNA and protein by 0.52-fold and 0.63-fold, respectively, and increased IL-10 protein by 2.74-fold after ALA intense pulsed light PDT.[20] In the past, PDT has been utilized with success,[22,23] and recently, more studies have shown variable results on its efficacy as a treatment of psoriasis.

There also have been attempts at using other photosensitizers for PDT in the treatment of psoriasis. One study evaluated methylene blue gel versus a placebo gel.[24] In the study, both gels were applied for 30 minutes followed by irradiation twice weekly using an LED with a wavelength of 670 nm and a power of 565 mW for 8 minutes at a fluence of 5 J/cm^2 until complete clearance of lesions or a maximum of 12 sessions. When treated with PDT, 19 of 23 enrolled patients showed complete clearance in

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lesions, 3 patients showed moderate to much degree of improvement, and 1 patient showed no improvement. The mean number of sessions was 9 to achieve complete clearance or improvement greater than 75%. Three patients reported tingling and tightness of the skin for 15 minutes posttreatment, and 1 patient reported hyperpigmentation, which resolved after topical application of hydroquinone cream 2% for 1 month. Sixteen patients still showed complete clearance of treated plaques 8 months posttreatment. In 2 patients, the treated plaques recurred after 3 to 4 months.[24]

Hypericin is a known photodynamic agent that has been demonstrated to induce apoptosis in normal and malignant B and T lymphocytes and has the potential to treat benign and malignant disorders of the skin, including psoriasis and cutaneous T-cell lymphoma.[25] A phase 2, placebo-controlled clinical study of 11 patients with psoriasis vulgaris demonstrated that hypericin in a liquid formulation was highly effective against psoriasis when applied topically at concentrations ranging from 0.1% to 0.25% followed by white light irradiation 24 hours later at 8 to 20 J/cm^2. The liquid formulation did not produce effects statistically better than placebo at any dose tested.[25]

Another study examined intravenous administration of the photosensitizer verteporfin (benzoporphyrin derivative monoacid ring A) and subsequent irradiation for 3 hours with a 600- to 700-nm light source at 60 J/cm^2 for a total of 5 weeks as a treatment of psoriasis.[26] In 5 of 20 (25%) participants, the study had to be prematurely terminated due to either thrombophlebitis, lack of compliance, intercurrent infection, or acute dermatitis from extravasation of verteporfin. The 15 (75%) remaining participants exhibited partial responses as early as 2 weeks after initiation of treatment. Improvement was noted in lesions that received the therapy compared with untreated control lesions.[26]

In addition to the investigation of various photosensitizers, there also have been investigations of pretreatments prior to PDT. A randomized, observer-blinded study demonstrated the benefits of keratolytic treatment prior to PDT.[27] Twenty-nine patients with chronic plaque-type psoriasis were treated with a keratolytic (salicylic acid 10% in white petrolatum) until all scales were removed or a maximum period of 2 weeks prior to PDT. Three psoriatic plaques in each patient were randomly allocated to PDT with ALA 1% and a light dose of 5, 10, or 20 J/cm^2, respectively, twice weekly until complete clearance or a maximum of 12 irradiations. Keratolytic pretreatment alone reduced the baseline psoriasis severity index (PSI [reflecting a summed score of scaling, erythema, and induration]) in all 3 dose groups by approximately 25%. Subsequent PDT with 20 J/cm^2 resulted in a 59% reduction in PSI; PDT with 10 and 5 J/cm^2 decreased the baseline PSI score by 46% and 49%, respectively. All patients reported some degree of stinging or burning during irradiation that, in some cases, lasted up to several hours. The authors concluded that topical ALA-PDT was an inadequate treatment option for psoriasis because of the unsatisfactory clinical response (complete clearance observed in only 8 of 63 [13%] treated lesions) and frequent occurrence of pain reported during and after irradiation.[27]

Schleyer et al[28] also did not find ALA-PDT to be a good treatment of psoriasis due to disappointing clinical efficacy and the time-consuming nature of the therapy. In a prospective, randomized, double-blind, phase 1/2 intrapatient comparison study on 12 patients with chronic plaque-type psoriasis, the mean percentage of improvement following ALA-PDT was 37.5%, 45.6%, and 51.2% in the 0.1%, 1%, and 5% ALA-treated groups, respectively.[28]

Beattie et al[29] also noted a negative outcome, reporting that plaques increased and persisted in 3 of 4 (75%) patients treated with weekly ALA-PDT applied to a single plaque under occlusion for 4 hours followed by irradiation with a diode laser at 10 J/cm^2, despite a reduced scaling, erythema, and induration (SEI) score in PDT-treated plaques. Fluorescence also was variable and unpredictable. As a result of the poor response and pain experienced, this trial was prematurely stopped.[29]

Fransson and Ros[30] also concluded that although a good clinical response was seen in most patients, the high frequency of discomfort experienced during treatment limited the usefulness of ALA-PDT for the treatment of psoriasis. Four of 12 (33%) psoriatic patients dropped out of the study because of pain during treatment. In the remaining 8 patients, 1 plaque was treated once weekly with PDT (10–30 J/cm^2) 2 to 5 times. Median SEI scores were significantly reduced from 7 (range, 5–9) to 1.5 (range, 0–3) following treatment ($P<.0001$). Also, cytokeratin 16 expression and CD4$^+$ and CD8$^+$ T cells in the dermis decreased.[30] Smits et al[31] also found that clinical improvement paralleled histologic improvement as seen in normalization of epidermal proliferation as well as differentiation and infiltration of relevant T-cell subsets.

Similarly, Robinson et al[32] concluded that ALA-PDT is unsuitable for treating psoriasis; although clinical efficacy improved with multiple treatments, there was an unpredictable response due to the varying intensity of ALA-induced protoporphyrin IX fluorescence of sites on the same patient as well as different patients, and there also was substantial patient discomfort. In 10 patients with plaque psoriasis, ALA-PDT was performed up to

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3 times per week for a maximum of 12 treatments using a light dose of 8 J/cm^2 delivered at a dose rate of 15 mW/cm^2. Of 19 treated sites, 4 (21%) cleared (only 1 fully), 10 (53%) responded but did not clear, and 5 (26%) showed no improvement.[32]

Collins et al[33] also reported a variable response in their study of 22 patients with plaque psoriasis treated with ALA-PDT. Eleven patients in group 1 received light doses of 2, 4, 8, and 16 J/cm^2 delivered at a fixed dose rate of 25 mW/cm^2; in group 2, 11 patients received light doses of 8 and 16 J/cm^2 delivered at both 10 and 40 mW/cm^2. In group 1, 10 of 36 (28%) treatment sites demonstrated clearance, 4 (11%) showed a 30% to 50% reduction in SEI score, and 22 (61%) showed minimal or no improvement. Clearance occurred between 11 and 17 days after treatment. In group 2, 4 of 44 (9%) sites cleared, 2 (5%) showed a 30% to 50% SEI score reduction, and 38 (86%) showed minimal or no improvement.[33]

Photodynamic therapy also has been suggested as a therapy for nail psoriasis. In a study by Fernández-Guarino et al,[34] 14 participants received treatment with PDT on one hand (61 nails) and PDL on the other hand (60 nails) once a month over 18 months. The hands treated with PDT were occluded with methyl-ALA for 3 hours using a bioadhesive patch prior to PDT. Nails were evaluated at baseline as well as at 3 and 6 months using the Nail Psoriasis Severity Index. A decrease in the Nail Psoriasis Severity Index score was observed with both treatments; however, no statistical differences were observed between the two.[34]

Another study demonstrated mild to marked improvement in 3 intractable cases of palmoplantar psoriasis treated with PDT using ALA 20% and a 630 +/− 50 nm LED device. The power density was 30 mW/cm^2 and the fluence was 15 J/cm^2.[35]

Although not as recent, and contrary to the negative conclusions of most studies investigating ALA-PDT as a treatment of psoriasis, Boehncke et al[36] found that PDT was efficacious in 3 patients with chronic plaque-stage psoriasis. Every other day, an ointment containing δ-ALA 10% was topically applied to a plaque lesion 5 hours before irradiation. The 600- to 700-nm light emitted by a 1200-W bulb was used for therapy (dose, 25 J/cm^2; power density, 70 mW/cm^2). Clearance of the PDT-treated lesions paralleled the response of those treated with dithranol. All patients noted moderate burning sensations. No other adverse side effects were noted over a 6-month follow-up.[36]

Overall, most of the data on PDT for the treatment of psoriasis are limited to small samples of patients and case reports; therefore, it is clear that large, double-blinded, randomized trials need to be performed to truly determine the role of PDT as a treatment option for psoriasis.

FUTURE DIRECTIONS

Except for the excimer laser, evidence for using other lasers to treat psoriasis, especially the Nd:YAG 1320-nm laser, the CO_2 laser, and PDT, is poor; only case reports and small trials have been published to date. Traditional therapies for psoriasis—topical vitamin D_3 analogues and corticosteroids—and light-based therapies such as NB-UVB and psoralen plus UVA appear to maintain their status in efficacy and tolerability when compared to more recent approaches involving lasers and other light treatments. Nevertheless, the manifestations of psoriasis are diverse and many patients present with lesions that are recalcitrant to traditional methods; hence, they are motivated to seek other options. In the future, there likely will be continued use of the 308-nm excimer laser to treat psoriasis, which often yields results that are clinically similar to NB-UVB but with a highly selective treatment zone.[37] The excimer laser has performed particularly well in treating palmoplantar and scalp variants compared to traditional therapies.[38] The results of PDL treatment also appear to be promising. The PDL often elicits a favorable response in refractory cases, may yield longer remission duration, and may be appropriate in nail manifestations. Photodynamic therapy has demonstrated mixed results that are mostly disappointing, but it may be advantageous when lesion size and distribution limits efficacy from other treatments. To date, the Nd:YAG and CO_2 lasers have been a less-appealing choice for treating psoriasis due to their side-effect profile and lackluster outcomes.

In the future, topical agents will continue to dominate the field of psoriasis treatment, followed by systemic and certain laser and light-based therapies. The PDL, Nd:YAG, and CO_2 lasers, as well as PDT, fall short of satisfactory results and will continue to be employed as alternatives when other treatment modalities fail. The 308-nm excimer laser and lamps (ie, monochromatic excimer light) as well as psoralen plus UVA and NB-UVB likely will continue to be employed as important adjuncts to topical treatment options. It is likely that future applications of laser and light approaches will be in combination with topical agents. For instance, Menter et al[39] described the use of methotrexate with UVB and acitretin with UVB therapy, which both showed promise in clinical efficacy and a reduction in dose-related toxicity. Similarly, Ablon[40] applied combination therapy that included treatment with both the 830- and 633-nm diode lasers in 9 patients, which demonstrated clearance rates ranging from 60% to 100% with excellent patient satisfaction and no reported side effects. Although this study is preliminary and small,

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it suggests that multiplex laser modalities are worthy of further study. Limiting factors that restrict broader use of laser therapies include the relatively high cost, the inconvenience of serial outpatient treatments, and the inability to treat extensive body surface areas. In the future, there also may be therapies that are directed at the level of antigen presentation, as current investigation is underway to pinpoint specific antigenic triggers. Ultimately, the pursuit of many treatment modalities will continue in addressing this common yet distressing disease.

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