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Treatment of Acne Vulgaris-Associated Post-Inflammatory Dyschromia With Combination of Non-Ablative Laser Therapy and Topical Antioxidants

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ABSTRACT

Acne can cause disfiguring sequelae, such as scarring, post-inflammatory erythema (PIE), and post-inflammatory hyperpigmentation (PIH). These post-inflammatory dyschromias pose a significant psychological burden on patients. This burden disproportionately affects skin of color (SOC) patients and can be the most distressing aspect of acne in SOC patients with skin types IV to VI. Multiple non-ablative lasers are used in the treatment of acne-related PIE and PIH. Combination therapies have shown promise in conditions such as rosacea, acne, and post-inflammatory dyschromia. Addressing both the inflammatory and scarring components of acne is key. Given the role of oxidation in the inflammatory cascade, including antioxidants could be an efficacious adjuvant with non-ablative lasers. This is a single-site, randomized, controlled clinical study of 25 subjects with skin types I to VI with facial PIE and/or PIH from acne. The primary objective was to investigate the clinical efficacy of non-ablative laser therapy followed by the topical application of Silymarin/Salicylic Acid/L-Ascorbic Acid/Ferulic Acid (SSAF) or control in the improvement in oily skin patients with facial PIE and PIH due to acne lesions. There was a statistically significant decrease in PIH and intralesional melanin in patients treated with a combination SSAF and non-ablative laser therapy. Improvement of both PIE and PIH was augmented in combination with SSAF and laser-treated patients compared with the laser-only group, with a concomitant increase in collagen density. This was even more strikingly marked in the SOC subjects, potentially providing an energy-based device (EBD)-based therapy in this population. Limitations of this study include small sample size and length of post-treatment follow-up.

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INTRODUCTION

Acne vulgaris (AV) is the most common inflammatory dermatosis worldwide. While it presents in 95% to 100% of men and 83% to 85% of women during puberty,[1] acne commonly extends into adulthood,[2] and can result in disfiguring sequelae such as scarring, post-inflammatory erythema (PIE), and post-inflammatory hyperpigmentation (PIH). This post-inflammatory dyschromia poses a significant psychological burden on acne patients, often accounting for greater concern than the original acne lesions, and reducing quality of life.[3] For this reason, the management and treatment of post-inflammatory dyschromia represents a large proportion of the clinical, emotional, and economic burden associated with AV.[4] Importantly, this burden most commonly and disproportionately affects skin of color (SOC) patients,[5] and can be the most distressing aspect of acne in SOC patients with Fitzpatrick skin phototypes IV to VI.[6,7]

A disease of the pilosebaceous unit, AV is a result of multiple different pathologic processes, ranging from increased sebum production, lipid oxidation, and free radical exacerbation in antioxidant-poor skin.[8] The resultant inflammatory cascade has been hypothesized to stimulate angiogenesis and melanogenesis that underlie PIE and PIH.[9,10] Recent observations have also implicated aberrant and long-term B-cell mediated inflammation in the development of post-inflammatory dyschromia and scarring following acne,[11] suggesting a new potential mechanistic arm for treatment and the role of combination therapy.[12] These dyschromias are amplified in phototypes rich in melanin, with some studies reporting PIH prevalence as high as 65% in Black patients and 48% in Hispanic patients, when compared with 25% PIH in White patients.[13] This is likely related to the greater number and size of melanosomes in SOC, which may be overstimulated in the setting of chronic inflammation.[14,15] Therefore, acne-related

post-inflammatory dyschromia can be difficult to treat, and is particularly recalcitrant in SOC, frequently requiring multi-modal regimens.[16]

Currently, energy-based devices (EBDs) are considered first-line treatments for dyschromias associated with acne vulgaris;[1] and multiple non-ablative lasers are routinely used in the treatment of acne-related PIE and PIH.[17] However, there remain limitations to single-modality treatment, and combination therapies have shown significant promise in dermatologic conditions such as rosacea, acne, and post-inflammatory dyschromia.[18] This is likely achieved through the targeting of multiple contributory pathophysiological pathways, and the synergistic effects of combination therapy. In one recent consensus statement regarding the treatment of acne with EBDs, the necessity of addressing both the inflammatory and scarring components of the disease was highlighted, underscoring the unique opportunity inherent to the treatment of acne and its sequelae.[1] With increasing recognition of the role of oxidation in the induction of the inflammatory cascade in acne and its associated dyschromia, antioxidants could prove an efficacious adjuvant therapy.[19]

Given these considerations, there remains an unmet need for an integrated treatment of post-inflammatory dyschromia of blemish-prone skin, as well as the inflammation that can perpetuate it. Therefore, the primary objective of this study was to assess the safety and efficacy of non-ablative laser therapy followed by the topical application of a Silymarin/Salicylic Acid/L-Ascorbic Acid/Ferulic Acid acne product (SSAF) compared with laser therapy alone for improving facial acne-induced PIE and PIH in oily skin patients – with a particular focus on SOC patients.

MATERIALS AND METHODS

Study Design and Patient Selection

This was a single-center, prospective, randomized-controlled study approved by an independent Institutional Review Board (IRB). Subjects with facial PIE and/or PIH from acne were selected for treatment with non-ablative laser therapy followed by the topical application of 0.5% Silymarin/0.5% Salicylic Acid/15% L-Ascorbic Acid/0.5% Ferulic Acid SSAF (Silymarin CF™; SkinCeuticals, Dallas, TX, USA), or vehicle control (glycol serum).

Inclusion criteria were male or female subjects of all skin phototypes (Fitzpatrick skin types I-VI) greater than eighteen years of age with facial PIE and PIH. An enrollment minimum of 16 patients with Fitzpatrick skin types III to VI was set, with at least 2 patients of every Fitzpatrick skin type (I-VI). Exclusion criteria included pregnancy, active lactation or nursing, known photosensitivity dermatologic disorders, and medical conditions resulting in delayed wound healing.

Informed consent was obtained and subjects were randomly assigned to receive 3 monthly treatment sessions with either a non-ablative laser followed by application of SSAF (treatment A), or a non-ablative laser followed by vehicle control (treatment B). Twenty-five total patients were enrolled.

Treatment Regimen

Over 12 weeks, subjects received 3 laser treatments at monthly intervals, followed by immediate application of either SSAF or control glycol serum. Both groups received application of the topical product or control immediately post-laser treatment, and were then instructed to use their assigned product regimen twice daily throughout the entire duration of the study. Either a 595 nm Pulsed Dye Laser (PDL) (Candela/Syneron Vbeam Pulse Dye Laser, Marlborough, MA, USA) for treatment of PIE, or 1927 nm Thulium Laser (Fraxel Dual 1550/1927 Laser System, Solta, Hayward CA) for treatment of PIH were chosen on the basis of the subject's lesions and skin type.

At initial visits, facial skin was examined and general health assessed to ensure that there were no contraindications to proceeding with the study treatment. Additionally, digital photography images were collected at baseline, week 4, week 8, and week 12 in order to provide a qualitative comparison of the face before and after treatments.

Assessment

Improvement of PIE and PIH was evaluated through multiple independent modalities, including Post-Acne Hyperpigmentation Index (PAHPI) and Global Aesthetic Improvement Scale (GAIS) blinded observation scoring, and Mexameter® (Evalulab Inc. Mount Royal, Quebec, Canada) erythema and melanin index values. Assessments were made based on standardized clinical photographs captured by the Visia® Skin Analysis system (Canfield Scientific, Fairfield, NJ) prior to initiation of therapy and 30 days following the final treatment.

Additionally, improvement of collagen density was assessed through optical coherence tomography (OCT) (VivoSight, Michelson Diagnostics Ltd., Kent, UK), while pain scores were evaluated through the Numerical Pain Rating Scale (NPRS). Safety was monitored by the investigator throughout the trial with pre- and post-treatment facial visual skin examinations, as well as adverse event reporting.

RESULTS

Twenty-five female and male adult subjects with facial PIE and/or PIH from acne were selected for treatment with non-ablative laser therapy followed by the topical application of SSAF or vehicle control (glycol serum). Ages of the subjects ranged from 21 to 61, and all skin types (Fitzpatrick skin types I-VI) were represented within the cohort, with the majority of patients (n=20) being skin types III to VI (Table 1).

TABLE 1.

Demographics and Pigmentation Disorder of the Overall Population	
Patient Demographics (N = 25)	
Sex	
Female	23 (88%)
Male	2 (12%)
Age (years)	
22-30	14 (56%)
31-50	9 (36%)
51-61	2 (8%)
Race	
Asian	1 (4%)
Black	6 (24%)
Hispanic or Latino	13 (52%)
White	5 (20%)
Fitzpatrick Skin Type	
I	2 (8%)
II	3 (16%)
III	7 (24%)
IV	7 (28%)
V	4 (16%)
VI	2 (8%)
Pigmentation Disorder	
Post-inflammatory hyperpigmentation	16 (64%)
Post-inflammatory erythema	9 (36%)

Of the 25 patients enrolled, 24 completed treatment. Moreover, 5 patients did not complete Mexameter measurements within the pre-defined follow-up window, and were thus excluded from analysis of change in levels of melanin or erythema. Fourteen subjects were randomly distributed to receive treatment A, and 10 subjects to receive treatment B.

Following treatment, subjects were first assessed with PAHPI and GAIS blinded observation scoring by 3 blinded experts, revealing an overall 1.38 average mean decrease in PAHPI score from 3.21 (overall disease severity – moderate dense/diffuse) to 1.83 (slightly noticeable-mild) across all treatment groups (Table 2). In patients receiving SSAF, there was an average PAHPI decrease from 3.18 to 1.74 (1.44 decrease) when compared with the laser-only group 3.25 to 1.97 (1.28 decrease), suggesting an improvement trend with SSAF-treated patients (Table 2). The GAIS score also showed overall improvement across 3 blinded observers, with an overall mean score of 3.24 (much improved) across all subjects, with a higher improvement score witnessed in patients receiving SSAF (3.35), when compared with laser-only (3.10; Figures 1-3).

FIGURE 1. Improvement of PIE in a 29-year-old female with FST III before (left) and after (right) 3 Pulsed Dye Laser treatments followed by immediate application of SSAF, and twice daily over 12 weeks.

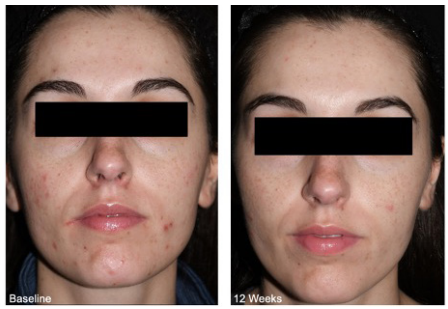


FIGURE 2. Improvement of PIH in a 33-year-old female with FST IV before (left) and after (right) 3 1927-nm Thulium Laser followed by immediate application of SSAF, and twice daily over 12 weeks.

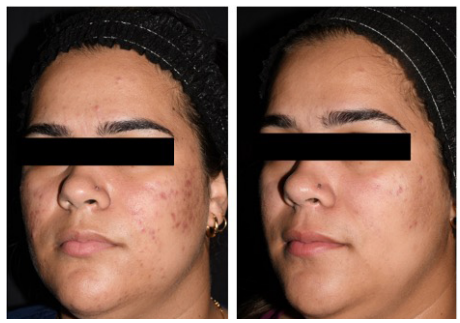
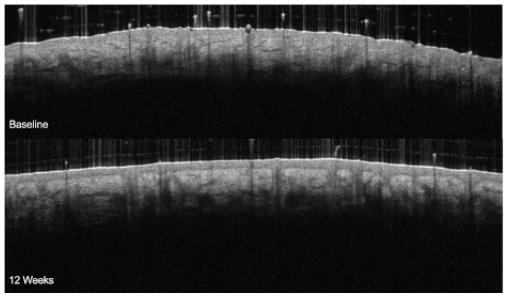


FIGURE 3. Improvement of PIH in a 27-year-old female with FST V before (left) and after (right) 3 1927-nm Thulium Laser followed by immediate application of SSAF, and twice daily over 12 weeks.

TABLE 2.

Comparing Means of Post-Acne Hyperpigmentation Index for Treatment Groups			
Post-Acne Hyperpigmentation Index	**Baseline**	**Final**	**Average**
	Mean Grade	**Mean Grade**	**Mean Decrease**
All 25 Patients	3.21	1.83	1.38
Silymarin & Laser Treatment	3.18	1.74	1.44
Laser Treatment	3.25	1.97	1.28

FIGURE 4. OCT image of increased collagen density in a patient before (top) and after (bottom) treatment with SSAF and non-ablative laser therapy.



PIH was then assessed with analysis of Mexameter index, and revealed a significantly significantly decreased mean level of intralesional melanin in patients treated with SSAF (39.76), when compared with laser only (P=0.02781, paired t-test). In enrolled subjects with Fitzpatrick skin types III to VI, there was a 34% decrease in melanin pigmentation after 12 weeks (Figures 2 and 3). These analyses were followed by tests of non-lesional, non-treated skin, which did not reveal a change in melanin levels. PIE was then similarly assessed without witnessed the difference between combination therapy and laser-only groups. Finally, OCT analysis demonstrated an increase in intensity at a depth of 0.2 mm in the papillary dermis of patients treated with SSAF and non-ablative laser therapy, corresponding to an increase in collagen density (Figure 4).

Safety Evaluation

There were no adverse events or long-term complications reported within the control or treatment groups. Pain was assessed through the NPRS, a well-validated and utilized score for subjective pain assessment comprised of scores ranging from 0 (no pain) to 10 (worst imaginable pain).

Among the 24 patients who received at least 2 treatments, the average NPRS was 0.31. Throughout the duration of the clinical trial, the overall NPRS score was 0 for all but 8 patients. In those 8 patients, the values ranged from 0 to 3, and did not differ significantly between treatments A and B. For the 14 patients who received treatment A, the average Pain Score Numerical Rating was 0.4, while the 10 patients who received treatment B had an average score of 0.16. Welch two sample t-test analysis did not confirm any significant difference in NPRS between the groups.

CONCLUSION

While the use of laser therapy in the treatment of post-inflammatory dyschromia is well-described, we report the first randomized controlled trial comparing the efficacy of combination therapy with EBDs and topical SSAF to EBDs alone. Importantly, this investigation centered primarily on the treatment of SOC, providing a potential therapeutic option for PIH in the skin phototypes it primarily burdens. Currently, post-inflammatory dyschromia is the third most common reason for SOC patients to present to dermatology.[20] Although the use of lasers in SOC has increased in the past decade due to safer laser wavelengths, the relative dearth of available data in darker skin types, as well as concern for PIH following laser therapy itself, have historically been major limitations to EBD use. For this reason, we focused on the treatment of Fitzpatrick skin types III to VI, for whom post-inflammatory dyschromia often presents a pronounced therapeutic challenge.

Overall, the study revealed a statistically significant decrease in PIH and intralesional melanin in patients treated with a combination SSAF and non-ablative laser therapy. Additionally, clinical improvement of both PIE and PIH was augmented in combination with SSAF and laser-treated patients when compared with the laser-only group, with a concomitant increase in collagen density. This was even more strikingly marked in the SOC subjects, potentially providing an EBD-based therapy in a population with darker skin phototypes.

Although patients receiving the control solution also demonstrated improvement with laser monotherapy, the enhanced clinical response in patients receiving SSAF highlights the benefit of integrated treatment. A compound derived from the milk thistle plant *Silybum Marianum*, Silymarin has been shown to prevent lipid oxidation and scavenge reactive oxygen species (ROS) in vitro, potentially inhibiting multiple components involved in the pathogenesis of acne vulgaris.[21] In combination with the established antioxidant and anti-inflammatory properties of salicylic acid, l-ascorbic acid, and ferulic acid, the topical application of Silymarin has the ability to improve acne, while simultaneously ameliorating post-inflammatory dyschromia.[22] This ability may be related to the underlying role inflammation has in the development of PIH and PIE. In one study investigating inflammatory gene expression in biopsies of acne patients, patients prone to scarring demonstrated a persistent and augmented inflammatory response in lesional and non-lesional skin when compared with patients not prone to scarring,[11] suggesting the importance of decreasing inflammation in post-acne changes. SSAF is believed to slow the inflammatory cascade, likely resulting in the observed improvement in treated subjects.

Finally, laser-assisted drug delivery and pretreatment have also been studied in the context of improving the cutaneous bioavailability of topical medications, by increasing the depth of penetration.[23] One recent study illustrated improved ex vivo delivery of topical antioxidants with non-ablative fractional laser pretreatment, showing 10- to 21-fold increases in uptake of vitamin C serums depending on the concentration in donor human skin tissue.[24] Therefore, combination treatment with

SSAF and non-ablative laser therapy could serve as a promising solution for decreasing inflammation, PIE, and PIH, specifically in oily, blemish-prone skin.

Limitations of this study include a small sample size and length of post-treatment monitoring and follow-up. Additional large, multi-center studies are required to better characterize and establish the pathophysiology underlying the connection between inflammation and the development of PIH and PIE. Finally, future work will focus on extending long-term follow-up in order to analyze the potential for scar prevention with initial improvement of post-inflammatory dyschromia in acne patients.

DISCLOSURES

JKH, RQ, and VA report no conflicts of interest. JW is a consultant for Sciton and has conducted clinical trials for Candela and SkinCeuticals. JW received a research grant from L'Oréal to conduct research presented in this manuscript.

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