


Split-Sided Chest Study of Skin Rejuvenation Comparing Low-Energy, 1,927-nm Thulium Fractional Laser Treatment Prior to Photodynamic Therapy Versus Photodynamic Therapy Alone

Jennifer Croix, Shannon Burge, Jennifer Chwalek, Robyn Gmyrek, and Anne Chapas ^{*}
 Union Square Laser Dermatology, 19 Union Square West, New York, New York, 10003

Background and Objectives: Treatment of photoaging and intrinsic aging of the chest, with the associated concerns of skin roughness, uneven pigmentation, laxity, atrophy, and telangiectasias, can be problematic because of the potential for worsened esthetic outcomes with existing treatments. This study assessed the efficacy and safety of using nonablative fractional laser therapy (FLT) pretreatment with photodynamic therapy (PDT) versus PDT alone for chest rejuvenation.

Study Design/Materials and Methods: In a randomized, evaluator-blinded, split-sided study, adult female patients with photodamage to the chest received three treatment courses over an 8-week period with follow-up visits at Weeks 12 and 20. FLT was applied to one side of the chest, randomly assigned at baseline, followed by aminolevulinic acid-based PDT, delivered using a thermal, short incubation, broad area technique, to both sides of the chest. In-person and photographic assessments were conducted using five-point scales to evaluate outcomes including rhytides, pigmentation, skin texture, and telangiectasias.

Results: Eleven adults completed the study, of whom 11 had improved scores for rhytides and 10 had improved scores for skin texture at Week 20. There was no significant difference in any efficacy outcome between FLT and PDT and standard PDT alone. The severity of adverse events was rated significantly greater with the combined FLT–PDT treatment vs PDT alone.

Conclusions: Significant improvements were observed vs baseline for both sides of the chest treated with FLT–PDT or standard PDT following three treatment sessions. No significant difference in efficacy was observed between treatment approaches, although adverse events were more severe on the FLT-pretreated side. This study was not registered as it qualified as a nonsignificant risk study. *Lasers Surg. Med.* © 2019 The Authors. *Lasers in Surgery and Medicine* Published by Wiley Periodicals, Inc.

Key words: aminolevulinic acid; photodynamic therapy; chest rejuvenation; rhytides; skin texture; pigmentation; erythema; nonablative fractional laser

INTRODUCTION

Photoaging of the chest from ultraviolet damage and intrinsic aging is a common problem in which the

appearance of rough skin with uneven pigmentation, laxity, atrophy, and the presence of telangiectasias often concerns patients [1,2]. Related skin pathologies, such as actinic keratosis (AK) on the chest, may be particularly problematic because of the potential for worsened esthetic outcomes, including hypopigmentation, uneven texture, and scars, with traditional aggressive treatments like cryotherapy or other destructive modalities [3]. Novel treatments that resolve precancerous lesions while also improving skin appearance are therefore in great demand, but exact treatment protocols need to be further delineated.

Current light-based strategies typically include a series of short treatments with either fractional laser therapy (FLT) or photodynamic therapy (PDT) [1,4–7]. Nonablative fractional lasers are generally better tolerated and require shorter healing times than more intense ablative fractional lasers [1,4,8]. FLT using a low-energy, 1,927-nm, nonablative thulium laser has been shown to improve the appearance of photodamage on the face, including the clearance of AKs [4]. PDT usually includes the use of a photosensitizing agent such as aminolevulinic acid HCl (ALA), a combination that has also been shown to improve skin appearance and clear AKs from the face and chest [2,6,9].

PDT using a topical solution of ALA 20% (Levulan[®] Kerastick[®]; DUSA Pharmaceuticals, Inc., Wilmington, MA)

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and have disclosed the following: AC is an investigator and advisory board member for Candela, and a consultant for Solta and Merz. She was previously an investigator for Endymed. SB was previously a consultant for Candela. JCr, JCh, and RG have no relevant disclosures. This study was funded by DUSA Pharmaceuticals, Inc.

Present address of Shannon Burge, InMode Aesthetics, Lake Forest, CA, USA.

Present address of Jennifer Croix, Illinois Dermatology Institute, Skokie, IL, USA.

*Correspondence to: Anne Chapas, Union Square Laser Dermatology, 19 Union Square West, 5th Floor, New York, NY 10003. E-mail: drchapas@unionderm.com

Accepted 22 October 2019

Published online 14 November 2019 in Wiley Online Library (wileyonlinelibrary.com).

DOI 10.1002/lsm.23178

and activation by 10 J/cm^2 of blue light (Blue Light Photodynamic Therapy Illuminator, BLU-U[®]; DUSA Pharmaceuticals, Inc.) is Food and Drug Administration–approved for spot treatment of minimally to moderately thick AKs of the face and scalp or AKs of the upper extremities [10]. This form of PDT has also attracted considerable attention for its use in skin rejuvenation of the face and other areas exposed to chronic sun damage, like the neck, décolleté, and the backs of the hands [6].

Although PDT was initially developed for the treatment of the face, it has been recognized that, because of anatomical differences in the target skin, specific adaptations to the treatment procedure may help to ensure efficacy is maintained when treating other anatomical areas [6]. Most notably, chest skin has a thicker stratum corneum than the face, which may reduce the absorption rate of topical photosensitizers in the lower layers of the epidermis and dermis [11]. Additionally, chest skin contains fewer sebaceous glands and other appendages than facial skin, which may result in slower re-epithelialization and prolonged erythema after treatment [6].

These histological differences from the face suggest pretreatment with an ablative or nonablative fractional laser, which improves the penetration of topical medication by creating small channels that can act as conduits for topically applied treatment, may be a useful complement to PDT on chest skin [6,12,13]. Fractional laser-assisted drug delivery is increasingly used to enhance topical drug uptake in the treatment of a wide range of skin conditions, including photodamage, neoplastic lesions, scars, and infections [8]. This approach may be advantageous given that resurfacing of facial skin with a nonablative fractional laser can itself improve the appearance of photodamage and AKs [4]. A low-energy, the nonablative fractional laser is also less invasive than ablative therapy [4], as ablative fractional resurfacing is often associated with pain during treatment, followed by several weeks of post-treatment crusting, erythema, and increased risks of scarring and dyspigmentation [14,15].

The objective of this study was to evaluate the efficacy and safety of pretreatment with a fractional, 1,927-nm thulium laser prior to ALA-based PDT (FLT–PDT), compared with ALA-based PDT alone, to rejuvenate photo-damaged chest skin in female adults.

MATERIALS AND METHODS

Study Design

This was a 20-week, single-center, repeat-dose, split-sided chest comparison study of FLT–PDT versus PDT alone (Fig. 1). Written informed consent was obtained from each patient. The study protocol, amendments, and informed consent were reviewed and approved by the institutional review board. The study was conducted according to the ethical principles outlined in the Declaration of Helsinki [16].

Patients

Patients were recruited from an existing database of patients at a US dermatology practice, through referrals,

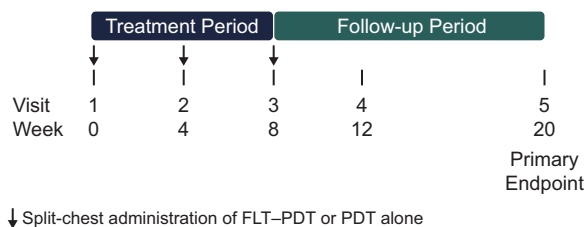


Fig. 1. Study design. FLT, fractional laser therapy; PDT, photodynamic therapy.

and through online recruitment. Eligible patients were women aged ≥ 18 years with Fitzpatrick skin type I–III and visible, moderate to severe photodamage to the chest, as indicated by rhytides, with a Fabi–Bolton score of II–IV [17]. Patients with a history of photosensitivity; patients with active infections or coagulation disorders; patients who were pregnant, lactating, or immunocompromised; patients receiving oral retinoids or photosensitizing drugs; and patients treated with topical retinoid therapy on the chest within 1 month of study entry were excluded. A full list of exclusion criteria can be found in the supplementary material.

Treatments

Eligible patients received a total of three treatment doses at Weeks 0, 4, and 8. FLT was applied to one side of the chest, randomly assigned at baseline using MS Excel 2011, with a fractional 1927-nm thulium laser (Permea; Solta Medical, Hayward, CA) at 5 mJ/microbeam and 5% coverage. Immediately following FLT, both sides of the chest were treated with topical ALA, which was occluded and heated using a heating pad for 30 minutes, followed by PDT consisting of 10 J/cm^2 of blue-light (417 nm) illumination for 1,000 s.

Endpoints and Assessments

Endpoints included both in-person assessments by a blinded treating physician and photographic assessments in which blinded dermatologists compared photographs of the individual, randomized chest areas from all patients in the study. The in-person assessments measured changes in rhytides and skin texture between an individual's chest sides from baseline to Week 20, as scored by the treating physician on a 5-point scale (absent/smooth, 1; severe, 5). The photographic assessments measured (i) change in pigmentation, fine lines and rhytides, redness, and telangiectasias from baseline to Week 20 (scored as a mean of three blinded dermatologist assessments using a 5-point scale: absent, 0; severe, 4) and (ii) change in overall improvement from baseline to Week 20 (based on blinded dermatologist ratings using a 5-point scale: no improvement, 0; 100% improvement, 4).

Assessment of Adverse Events

Adverse events, including erythema, edema, crusts and erosions, and burning/stinging sensations, were assessed immediately after treatment at each treatment visit and

were scored by the treating physician on a 5-point scale from none (0) to severe (4). Potential transient events associated with dermatological laser treatment, including bleeding, crusting, numbness, itching, and dryness, were considered a treatment response and not an adverse device effect.

Sample Size and Statistical Analysis

The statistical significance of the differences between treatments was evaluated by a two-sided paired *t* test. Power to detect calculations confirmed that a sample size of 11 patients was required for establishing 90% statistical power to reject the null hypothesis that FLT-PDT provides no benefit over PDT alone.

RESULTS

Patient Population

The study was conducted between October 2015 and August 2016. A total of 14 adult female patients were screened, met the entry criteria, and were enrolled in the study. Of those, 11 patients aged 53–72 years completed all three treatments and all three, monthly follow-up visits. Three patients left the study because of withdrawing consent (not related to adverse events). An overview of baseline patient demographics and clinical characteristics is presented in Table 1.

Efficacy Outcomes—In-Person Assessments

In-person blinded assessments of rhytides and skin texture showed significant improvement (≥ 1 -point increase) from baseline to Week 20 for both PDT alone and FLT-PDT (Fig. 2a and b). All 11 patients (100%) showed an improvement in scores for rhytides. Ten of 11 patients (91%) showed an improvement in scores for skin texture.

When comparing the degree of improvement from baseline to Week 20 with FLT-PDT versus PDT alone, there was no significant difference in mean improvement in rhytides (+1.55 vs. +1.46 points, respectively)

TABLE 1. Baseline Demographics and Clinical Characteristics

	Patients (N = 11)
Age, mean (range), y	61 (50–72)
Sex, n (%)	
Female	11 (100)
Race, n (%)	
White	11 (100)
Fitzpatrick skin type, n (%)	
I	5 (45)
II	3 (27)
III	3 (27)
Fabi-Bolton chest rhytide score, n (%)	
II	2 (18)
III	4 (36)
IV	5 (45)
V	0

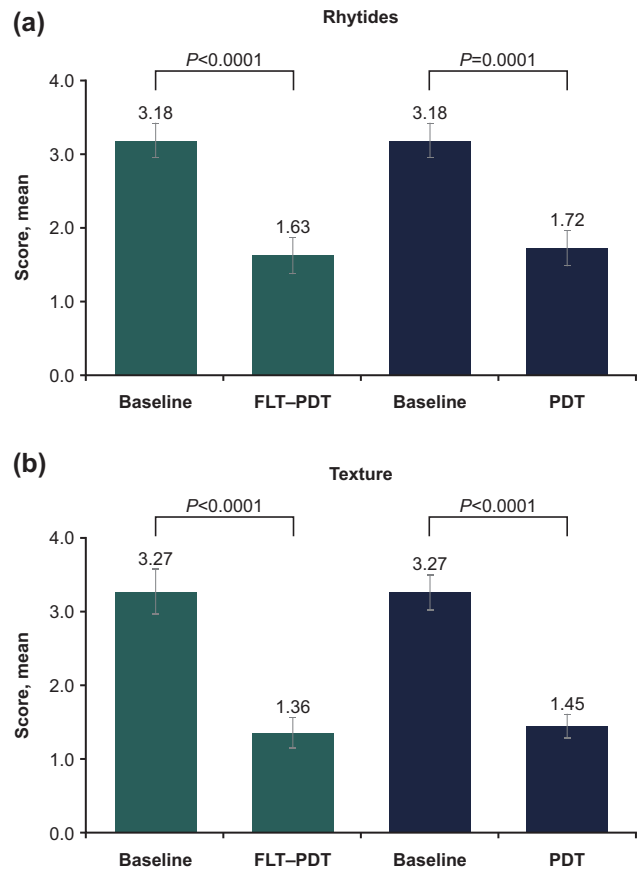


Fig. 2. Mean (SE) patient scores for chest (a) rhytides and (b) texture based on in-person blinded assessments at baseline and Week 20. FLT, fractional laser therapy; PDT, photodynamic therapy; SE, standard error.

or skin texture (+1.91 vs. +1.82 points, respectively) between the treatments.

Efficacy Outcomes—Photographic Assessments

Blinded assessments of photographs showed small but statistically significant improvements from baseline to Week 20 in rhytides, pigmentation, and erythema scores for both FLT-PDT and PDT alone (Fig. 3a–c). Baseline and Week 20 photos for four patients can be found in Figure 4.

Comparison of the degree of overall improvement from baseline to Week 20 with FLT-PDT versus PDT alone showed no significant difference (+1.73 vs. +1.94 points, respectively; $P = 0.13$). Comparison of improvements in erythema scores from baseline to Week 20 for FLT-PDT versus PDT alone showed a trend toward improvement for FLT-PDT versus PDT alone; however, this difference also was not statistically significant (+0.52 vs. +0.30 points, respectively; $P = 0.70$). There was no difference between the treatments in the extent of improvement from baseline to Week 20 in rhytides (+0.21 vs. +0.21 points) or pigmentation (+0.64 vs. +0.64 points) for FLT-PDT and PDT alone, respectively.

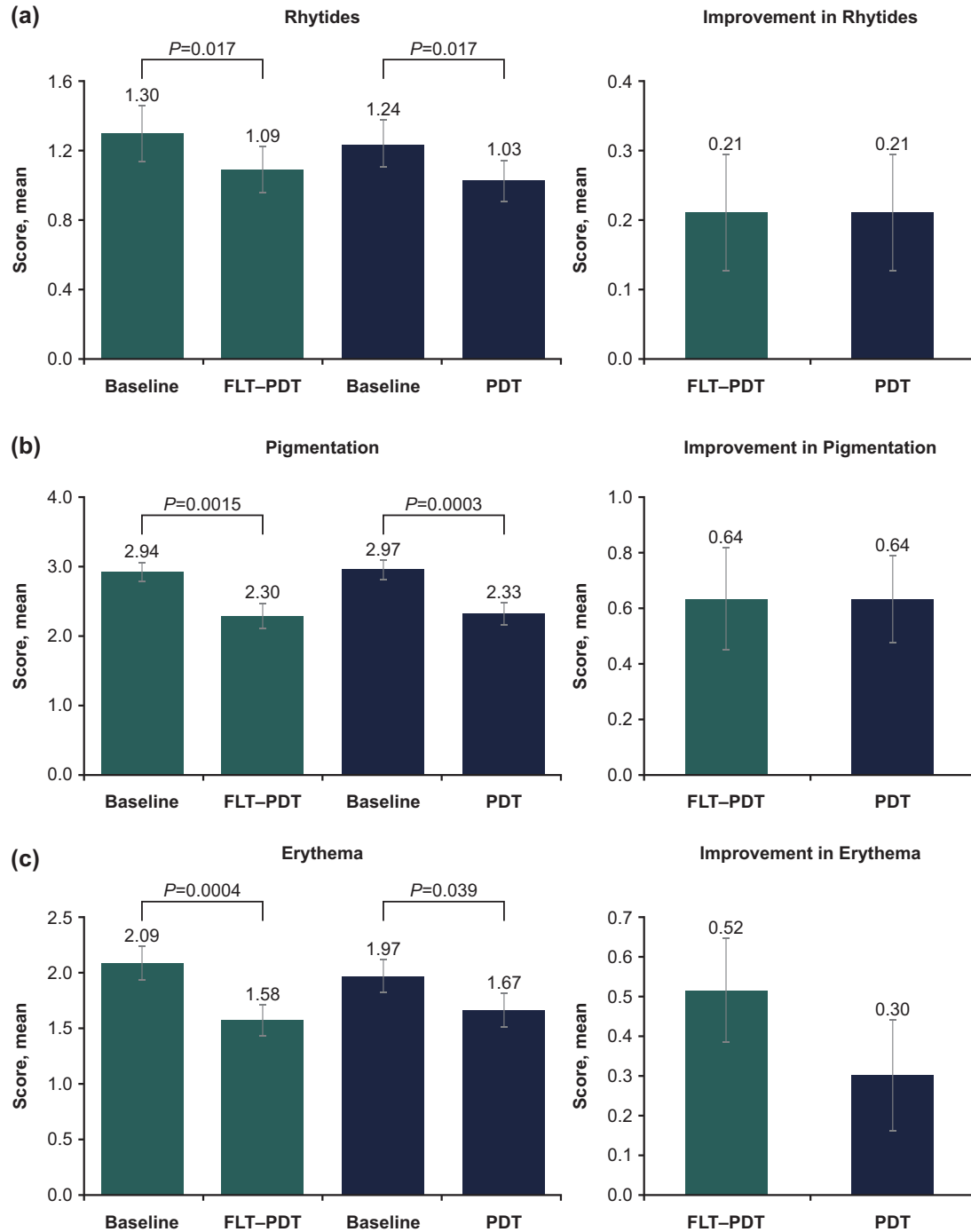


Fig. 3. Mean (SE) patient scores for chest (a) rhytides, (b) pigmentation, and (c) erythema/telangiectasias at baseline and Week 20 and improvements based on photographic blinded assessments from baseline to Week 20. FLT, fractional laser therapy; PDT, photodynamic therapy; SE, standard error.

Safety

The severity of post-treatment adverse events was significantly greater with FLT-PDT versus standard PDT alone (Fig. 5). The overall incidence of post-treatment erythema (all three treatment sessions combined; 33

assessments in total) was high after both treatments. Erythema occurred after 100% (33/33) of FLT-PDT treatment sessions, with an overall mean (standard error [SE]) rating of 3.24 (0.12), compared with 97.0% (32/33) of treatments with PDT alone, which had an overall mean (SE) rating of 1.39 (0.12; $P < 0.0001$) (Fig. 6).



Fig. 4. Baseline and Week 20 photographs for four patients receiving PDT only versus FLT-PDT. FLT, fractional laser therapy; PDT, photodynamic therapy.

Pain, rated as a burning or stinging sensation, was reported more frequently after the combination treatment versus treatment with PDT alone. In total, 84.8% (28/33) of FLT-PDT sessions caused burning or stinging, resulting in an overall mean (SE) rating of 1.45 (0.15), compared with 36.4% (12/33) and an overall mean (SE) rating of 0.55 for PDT alone ($P < 0.0001$). Edema was also more frequent after the combination treatment versus PDT alone, reported after 39.4% (13/33) of FLT-PDT sessions, resulting in a mean (SE) overall rating of 0.94 (0.23), compared with 21.2% (7/33) of standard PDT sessions, with a mean (SE) overall rating of 0.24 (0.09; $P = 0.0006$). One patient experienced crusting after the third treatment; graded as 1 for both sides of the chest.

One patient (9%) experienced postinflammatory hyperpigmentation (PIH) that was evident from Week 4 (Fig. 7), but this had resolved by Month 6 with a 16-week treatment of twice-daily hydroquinone 4% cream. PIH in this individual was evident on both treatment sides but was notably more severe on the side of the chest treated with FLT-PDT.

DISCUSSION

This investigation on the benefit of pretreating chest skin with FLT prior to ALA-based PDT, with the aim of enhancing the efficacy of PDT treatment, showed that there was no significant improvement in efficacy using this approach with the settings used in this study. The overall benefit-to-risk ratio of the procedure was reduced, as the combination of FLT pretreatment and PDT did not provide an improvement in efficacy over PDT alone, and there was an increase in the severity of adverse events.

Both the FLT-PDT combination treatment and PDT alone significantly improved outcomes for rhytides and skin texture from baseline to Week 20, with all but one patient showing an improvement in both measures, indicating that the FLT pretreatment did not alter the efficacy of the PDT treatment. The photographic assessments also showed significant improvements with both treatments approaches in chest rhytides, pigmentation, and erythema/telangiectasias over the 20-week study.

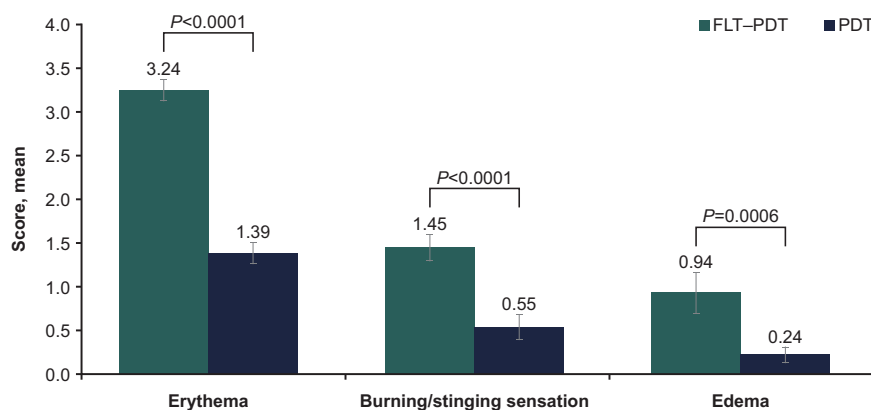


Fig. 5. Mean (SE) scores for immediate, post-treatment adverse events. FLT, fractional laser therapy; PDT, photodynamic therapy; SE, standard error.

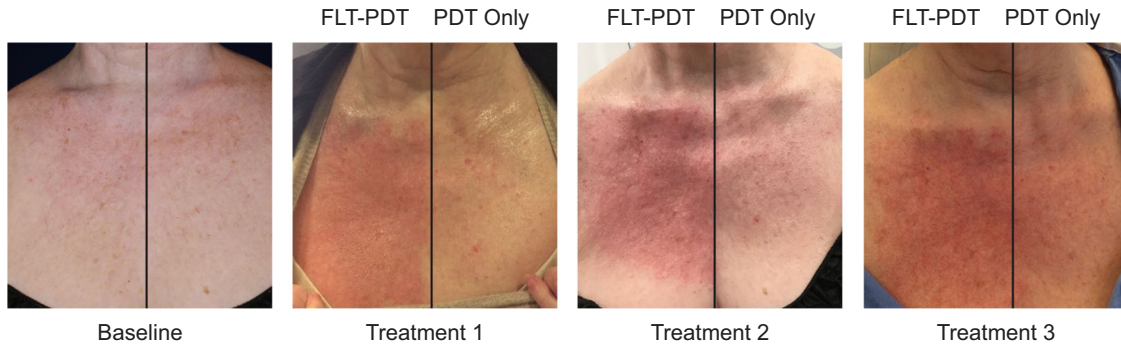


Fig. 6. Post-treatment adverse event of erythema. FLT, fractional laser therapy; PDT, photodynamic therapy.

However, both the in-person and photographic assessments failed to show any significant difference in these efficacy outcomes between treatment approaches, demonstrating that the efficacy of the PDT treatment was not meaningfully enhanced by the FLT pretreatment.

The most striking difference between treatment approaches was that the adverse events observed immediately after treatment were significantly more severe with FLT-PDT combination treatment compared with PDT alone. Erythema, which is an expected adverse effect of laser treatment, was observed in almost all patients immediately after treatment but FLT-PDT combination therapy had a higher overall mean severity score than PDT alone. Post-treatment burning or stinging sensations and edema were more common after FLT-PDT treatment than with PDT alone. PIH was evident in one patient and appeared worse on the side of the chest that underwent FLT pretreatment; however, the PIH had resolved by the Month-6 follow-up appointment.

It was not surprising that PDT with FLT pretreatment was efficacious in improving chest skin, given that both PDT and FLT are known to improve the appearance of photodamage on the face [4,5,7,18,19]. The lack of additional benefit in efficacy with FLT-PDT suggests that, as seen in a recent study of PDT pretreatments, even if higher protoporphyrin IX fluorescence levels are achieved, this does not necessarily result in greater efficacy [15]. Overall, a similar mode of action or mechanism of response is likely at the cellular level

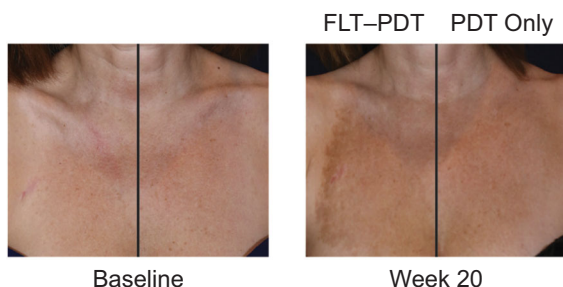


Fig. 7. Post-treatment adverse event of postinflammatory hyperpigmentation. FLT, fractional laser therapy; PDT, photodynamic therapy.

owing to the PDT on both treatment sides. A longer follow-up period may have offered further insight into any advantage conferred by FLT pretreatment.

A recent review by Juhasz et al. [19] reported that developments in the combination of PDT with FLT have allowed for enhanced dermal penetration of topical photosensitizers, including ALA and methyl aminolevulinic acid (MAL). This has led to increased efficacy of PDT treatment [13,20]. Additional novel methods for enhancing the penetration of either ALA or MAL photosensitizers in human skin prior to PDT include the combination of sonophoresis with fractional CO₂ laser or sonophoresis with radiofrequency [21,22].

Pretreatment of field-cancerized skin with a fractional CO₂ laser before MAL-based PDT has shown some potential for reducing the time required for occlusion with the photosensitizer [23]. Yet, in line with the main finding of our study, this approach did not have a significant impact on efficacy outcomes, in this case, the development of new AKs. Nonablative fractional laser pretreatment before daylight PDT (dPDT) with MAL has been investigated vs dPDT alone in the treatment of moderate to severe facial acne vulgaris [24]. Similarly, there was no significant difference in mean lesion counts between patients who received laser pretreatment and those who received dPDT alone; however, a significantly higher pain score was reported at the first visit by those receiving laser treatment [24]. A real-world case series on the use of a similar nonablative fractional laser for photothermolysis prior to ALA-PDT for the treatment of acne vulgaris reported improved outcomes with this approach, including minimal adverse events and a reduced need for treatment sessions compared with ALA-PDT alone [25].

Ablative fractional laser-assisted dPDT is a similar novel combination approach that has been investigated for the treatment of AKs in organ transplant recipients [26]. The study by Togsverd-Bo et al. [26] reported that the ablative pretreatment increased the percentage of complete responses at 3 months post-treatment compared with dPDT and conventional PDT alone. Erythema and crusting were more severe following ablative fractional laser-pretreated dPDT than after either dPDT or conventional PDT, with only transient hypopigmentation

observed [26]. Ablative FLT prior to PDT has also been trialed as a potential improvement to standard PDT for nodular basal cell carcinomas [27]. Similar to our study, results did not show a significant improvement in overall long-term efficacy for pretreated patients vs patients who received PDT alone. Therefore, ablative FLT has not been recommended over standard PDT for the treatment of basal cell carcinoma [27]. Ablative fractional laser-assisted PDT using MAL has also been demonstrated to provide long-term efficacy in a case study of lower extremity Bowen's disease [28].

One limitation of our study is its small sample size, although it was calculated that the study had adequate power to detect a statistical difference. Additionally, these results have limited generalizability to everyday clinical practice, given the study conditions in which the treatments were administered and monitored and the variety of skin types and photoaging processes that exist. Another potential aspect of the study that may impair direct comparison with other laser studies is that events typically considered to result from standard laser therapy, such as blistering and dryness, were classified as adverse effects in this study and therefore not listed under adverse events to provide a more sensitive evaluation of the differences between treatment approaches.

CONCLUSION

This study shows that the pretreatment of female chest skin with FLT prior to ALA-based PDT for aging-related skin disorders does not provide any meaningful improvements in efficacy outcomes compared with standard PDT alone. The tolerability of the overall procedure is reduced with FLT pretreatment, with an increase in the severity of adverse events versus PDT alone. The results indicate, however, that PDT alone and with pretreatment is efficacious at improving the appearance of rhytides, skin texture, pigmentation, and erythema in this patient population, suggesting that further studies may provide additional evidence that both FLT-PDT and PDT are efficacious for chest rejuvenation. Longer-term studies in larger populations are warranted to validate these results and help to establish any benefits of FLT-PDT over PDT alone.

ACKNOWLEDGMENTS

This study was funded by DUSA Pharmaceuticals, Inc. The authors would like to thank the patients and caregivers who took part in this study. Editorial support was provided by JK Associates, Inc., part of the Fishawack Group of Companies, and was funded by Sun Pharmaceutical Industries, Inc.

REFERENCES

- Peterson JD, Goldman MP. Rejuvenation of the aging chest: A review and our experience. *Dermatol Surg* 2011;37(5):555–571.
- Peterson JD, Kilmer SL. Three-dimensional rejuvenation of the décolletage. *Dermatol Surg* 2016;42(Suppl 2):S101–S107.
- Costa C, Scalvenzi M, Ayala F, Fabbrocini G, Monfrecola G. How to treat actinic keratosis? An update. *J Dermatol Case Rep* 2015;9(2):29–35.
- Weiss ET, Brauer JA, Anolik R, et al. 1927-nm fractional resurfacing of facial actinic keratoses: A promising new therapeutic option. *J Am Acad Dermatol* 2013;68(1):98–102.
- Nootheti PK, Goldman MP. Aminolevulinic acid-photodynamic therapy for photorejuvenation. *Dermatol Clin* 2007;25(1):35–45.
- Szeimies RM, Lischner S, Philipp-Dormston W, et al. Photodynamic therapy for skin rejuvenation: Treatment options — results of a consensus conference of an expert group for aesthetic photodynamic therapy. *J Dtsch Dermatol Ges* 2013;11(7):632–636.
- Gold MH, Goldman MP. 5-aminolevulinic acid photodynamic therapy: Where we have been and where we are going. *Dermatol Surg*. 2004;30(8):1077–1084.
- Wenande E, Erlendsson AM, Haedersdal M. Opportunities for laser-assisted drug delivery in the treatment of cutaneous disorders. *Semin Cutan Med Surg* 2017;36(4):192–201.
- Piacquadio DJ, Chen DM, Farber HF, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: Investigator-blinded, phase 3, multicenter trials. *Arch Dermatol* 2004;140(1):41–46.
- DUSA Pharmaceuticals. Levulan® Kerastick® (aminolevulinic acid HCl) for topical solution, 20% [package insert]. Wilmington, MA. 2018.
- Ya-Xian Z, Suetake T, Tagami H. Number of cell layers of the stratum corneum in normal skin—Relationship to the anatomical location on the body, age, sex and physical parameters. *Arch Dermatol Res* 1999;291(10):555–559.
- Haedersdal M, Sakamoto FH, Farinelli WA, Doukas AG, Tam J, Anderson RR. Fractional CO₂ laser-assisted drug delivery. *Lasers Surg Med* 2010;42(2):113–122.
- Togsverd-Bo K, Haak CS, Thaysen-Petersen D, Wulf HC, Anderson RR, Haedersdal M. Intensified photodynamic therapy of actinic keratoses with fractional CO₂ laser: A randomized clinical trial. *Br J Dermatol* 2012;166(6):1262–1269.
- de Vries K, Prens EP. Laser treatment and its implications for photodamaged skin and actinic keratosis. *Curr Probl Dermatol* 2015;46:129–135.
- Bay C, Lerche CM, Ferrick B, Philipsen PA, Togsverd-Bo K, Haedersdal M. Comparison of physical pretreatment regimens to enhance protoporphyrin IX uptake in photodynamic therapy: A randomized clinical trial. *JAMA Dermatol* 2017;153(4):270–278.
- World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Bull World Health Organ* 2001;79:373–374.
- Fabi S, Bolton J, Goldman MP, Guiha I. The Fabi-Bolton chest wrinkle scale: A pilot validation study. *J Cosmet Dermatol* 2012;11(3):229–234.
- Alexiades-Armenakas M. Aminolevulinic acid photodynamic therapy for actinic keratoses/actinic cheilitis/acne: Vascular lasers. *Dermatol Clin* 2007;25(1):25–33.
- Juhász ML, Levin MK, Marmur ES. The two faces of fractionated photodynamic therapy: Increasing efficacy with light fractionation or adjuvant use of fractional laser technology. *J Drugs Dermatol* 2016;15(11):1324–1328.
- Ko DY, Jeon SY, Kim KH, Song KH. Fractional erbium: YAG laser-assisted photodynamic therapy for facial actinic keratoses: a randomized, comparative, prospective study. *J Eur Acad Dermatol Venereol* 2014;28(11):1529–1539.
- Choi JH, Shin EJ, Jeong KH, Shin MK. Comparative analysis of the effects of CO₂ fractional laser and sonophoresis on human skin penetration with 5-aminolevulinic acid. *Lasers Med Sci* 2017;32(8):1895–1900.
- Park JM, Jeong KH, Bae MI, Lee SJ, Kim NI, Shin MK. Fractional radiofrequency combined with sonophoresis to facilitate skin penetration of 5-aminolevulinic acid. *Lasers Med Sci* 2016;31(1):113–118.
- Vrani F, Sotiriou E, Lazaridou E, et al. Short incubation fractional CO₂ laser-assisted photodynamic therapy vs. conventional photodynamic therapy in field-cancerized skin: 12-month

- follow-up results of a randomized intraindividual comparison study. *J Eur Acad Dermatol Venereol* 2019;33(1):79–83.
24. Kim TI, Ahn HJ, Kang IH, Jeong KH, Kim NI, Shin MK. Nonablative fractional laser-assisted daylight photodynamic therapy with topical methyl aminolevulinate for moderate to severe facial acne vulgaris: Results of a randomized and comparative study. *Photodermatol Photoimmunol Photomed* 2017;33(5):253–259.
 25. Qureshi S, Lin JY. Utilizing non-ablative fractional photothermolysis prior to ALA-photodynamic therapy in the treatment of acne vulgaris: A case series. *Lasers Med Sci* 2017; 32(3):729–732.
 26. Togsverd-Bo K, Lei U, Eriendsson AM, et al. Combination of ablative fractional laser and daylight-mediated photodynamic therapy for actinic keratosis in organ transplant recipients—A randomized controlled trial. *Br J Dermatol* 2015;172(2):467–474.
 27. Haak CS, Togsverd-Bo K, Thaysen-Petersen D, et al. Fractional laser-mediated photodynamic therapy of high-risk basal cell carcinomas—A randomized clinical trial. *Br J Dermatol* 2015;172(1):215–222.
 28. Jung SE, Kim SK, Kim YC. Photodynamic therapy in Bowen disease of the first web space of the hand. *Ann Dermatol* 2015;27(1):76–78.