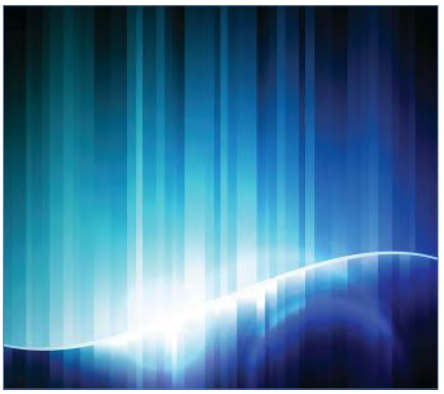

Biophotonic Therapy with Fluorescent Light Energy Decreases Facial Erythema, Improves Signs and Symptoms of Rosacea, and Increases Patient Satisfaction: A Postmarket Study

by MARTIN WADE, BMed Sci, MBBS, FACD; VANESSA CHAREST, BSc, BRUNO BALLARDIN, B. Eng, MBA; DEIRDRE EDGE, PhD; and MICHAEL CANOVA ENGELBRECHT NIELSEN, PhD

Dr. Wade, Ms. Charest, and Mr. Ballardin are with the London Skin and Hair Clinic in London, England. Drs. Edge and Nielsen are with Guangdong Klox Biomedical Group Co., Ltd., in Guangzhou, China.

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ABSTRACT

BACKGROUND: Rosacea is a difficult-to-manage chronic inflammatory skin condition reported to have a negative psychosocial impact on patients. Novel approaches are sought to target the many signs and symptoms of the condition while also improving the quality of life of patients. **OBJECTIVE:** We assessed the efficacy of the Kleresca® biophotonic platform (KLOX Technologies Inc., Laval, Canada), which creates fluorescent light energy (FLE), to induce a novel form of photobiomodulation for treating rosacea. We also assessed patient satisfaction with their facial appearance and concerns about perceptions of others before and after treatment. **METHODS:** Nine patients were treated once a week for four weeks with FLE. Patients and the treating clinician completed questionnaires throughout and after the treatment to grade the rosacea signs and symptoms and capture patients' perceptions of the treatment and their condition. **RESULTS:** FLE significantly reduced the inflammatory erythematous reaction of the face, improved flushing and erythema associated with rosacea, and had a positive impact on patients' self-perception and emotional wellbeing. **CONCLUSION:** Our results support FLE as an effective, noninvasive treatment modality for rosacea.

KEY WORDS: Rosacea, erythema, flushing, questionnaire, biophotonics, chromophore, fluorescent light energy, inflammatory skin conditions, FLE, photobiomodulation, skin quality, patient perception, quality of life

Rosacea is a chronic inflammatory skin condition affecting both men and women, with high incidence rates in those with Fitzpatrick Skin Types I and II.[1] Often underdiagnosed, it is estimated to affect approximately 5.5 percent of the population worldwide.[2] While the etiology of rosacea is evolving, it is understood that an aberrant immune response, altered neurovascular signalling, and colonization of the skin with microorganisms (i.e., *Demodex folliculorum*) all play a role.[1] Common features of rosacea include flushing, nontransient erythema, papules, pustules, telangiectasia, burning or stinging, and skin sensitivity.[3] Rosacea has typically been classified into four main subtypes, erythematotelangiectatic (ETR), papulopustular (PPR), phymatous, and ocular, depending on the presentation.[3] However, with updates to this classification system, it has emerged that patients often present with a variety of clinical features characteristic of more than one subtype.[4] Further, major fixed centrofacial erythema is a main diagnostic feature[5] and common among all presentations of rosacea.[6,7]

Effectively targeting erythema has posed a challenge in treating rosacea.[8] Since a single patient with rosacea can have a variety of clinical features, a combined treatment approach is often prescribed. Current treatment options often include topical creams, systemic treatments, and laser and light therapy to target the broad spectrum of phenotypes of the condition.[9] However, results are varied, with either low adherence or limited patient satisfaction.[10,11]

In addition to the physical aspects of rosacea, there is a significant psychosocial burden associated with the condition. Patients report low self-esteem, embarrassment, frustration, and affected professional interactions.[10,12] Furthermore, rosacea is linked to depression and has significant effects on patients' quality of life (QoL).[12,13] There is currently no cure for rosacea; therefore, treatment options that can manage the signs and symptoms, halt progression, and improve the patient's QoL are required.

Previous reports with the Kleresca® biophotonic platform (KBP; KLOX Technologies Inc., Laval, Canada) have been promising in not only treating rosacea signs and symptoms in rosacea subtypes 1, 2, and 3, but also in improving the visible appearance of the skin.[14,15] This postmarket study sought to assess the therapeutic efficacy of the KBP while also capturing the patient and clinician perceptions of the condition and the effect of the treatment.

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CORRESPONDENCE: Michael Canova Engelbrecht Nielsen, PhD; Email: men@kloxasia.com

METHODS

Patients with rosacea subtype 1 (ETR) and subtype 2 (PPR) were recruited by the treating clinic to receive the treatment. At the initial consultation, the treating practitioner completed a patient information and first assessment form. The treatment procedure was conducted as per the manufacturer's instructions for use. Briefly, a 2-mm layer of the proprietary chromophore-containing gel was applied to the cleansed face and illuminated with a multi-light-emitting diode lamp for nine minutes, once per week for four consecutive weeks (note: one patient had a three-week break between the first and second treatments due to work commitments). Patients were brought back to the clinic for a follow-up visual assessment at between eight and 12 weeks from initiation of the treatment (mean±standard error of the mean time: 9.5±0.6 weeks).

Patients had their photo taken (VISIA® System; Canfield Scientific, Fairfield, New Jersey) and both the patients and the treating practitioner completed a questionnaire before every treatment and at the follow-up session. Patient questions were partly adapted from research by Zeichner et al[10] addressing the severity of rosacea signs and symptoms (intensity: graded as 0=absent, 1=mild, 2=moderate, or 3=severe). The skin's appearance was graded from 0 to 10, where 0=very bad and 10=excellent. An initial assessment specifically investigating patients' satisfaction with their facial appearance and concerns about others' perceptions was evaluated using a five-point Likert scale (1=strongly disagree, 2=disagree, 3=neither agree nor disagree, 4=agree, 5=strongly agree) and was completed before the first treatment and repeated after the four treatments. All patients participated on a voluntary basis and provided informed consent before the initiation of the study. Clinician questions focused on grading the rosacea signs and symptoms as well as the overall appearance of the skin.

Participants. The demographics of the study participants are outlined in Table 1. Nine patients completed the four treatment sessions to the follow-up phase. The mean age was 36±3 years and, of the nine patients, 78 percent were female and 22 percent male, diagnosed 31±13 months ago. PPR was the predominant rosacea subtype, with 80 percent of patients presenting, while 20 percent had ETR. Participants had previously tried a variety of treatments, including topical creams (e.g., ivermectin, metronidazole, and elidel) and antibiotics. Participants were not undergoing any treatment that would interfere with results during the study.

Data analysis. Questionnaire data were coded and manually entered into Microsoft Excel (Microsoft Corporation, Redmond, Washington). Frequency and percentages were used to summarize data where relevant. Otherwise, per question, data were averaged for all participants in each session (i.e., Week 1, Week 4, etc.) and compared across sessions. Nonresponsive data (left blank) were treated in the same as "neither," where applicable. Data were compared using a repeated-measures one-way analysis of variance with Tukey's multiple comparison or paired Student's t-test as necessary (GraphPad version 8; GraphPad Software Inc., San Diego, CA, USA). Data are expressed as mean±standard error of the mean values and $p<0.05$ was considered to be statistically significant.

For patient image analysis, a standardized area of all (baseline, Week 4, and follow-up) patient VISIA® photos (red, green, and blue; RGB) was selected in a uniform manner and cropped using ImageJ (v.1.51u; National Institutes of Health, Bethesda, Maryland). In the cropped part of the photo, the blue and green channels were removed from the RGB and the remaining red channel was converted into a graphic interchange format (GIF), allowing for a frequency distribution of the redness of the pixels to be calculated (0–256 bins of red pixels) (Figure 1A).

Subsequently, the frequency distribution was analyzed to determine the change in the redness. This was assessed by a shift in the pixel bin frequency, whereby a shift towards a higher distribution in lower bins represented a reduction in facial redness and vice versa. Images were compared using repeated-measures two-way analysis of variance using the Greenhouse-Gaisser correction for an overall change in the distribution (intensity) of red pixels among the three time points (baseline, during treatment, and follow-up).

TABLE 1. Patient demographics

Number of participants	9
Age (years), mean ± SEM	36±3
Rosacea subtype	
1	20%
2	80%
Fitzpatrick Skin Type	
II	70%
III	30%
Sex (n)	
Female	7
Male	2
First signs (months), mean ± SEM	57±22
Diagnosed (months), mean ± SEM	31±13

SEM: standard error of the mean

RESULTS

Facial redness. There was a significant overall decrease in facial redness both during the treatment period and in the follow-up period relative to at baseline for all patients combined (n=9) ($p<0.001$). This was represented by a leftward shift in the frequency distribution of the intensity of red pixels (decreased intensity) for both, in treatment (four-week time point) and the follow-up period for each patient (Figure 1B). Baseline pixel distribution pattern was comparable for all patients at each sampling point.

Rosacea signs and symptoms questionnaire data. Patient self-assessment reported that the intensity of flushing and redness were significantly decreased following treatment ($p=0.029$ and $p=0.022$, respectively, one-way analysis of variance) (Figure 2A) at the four-week time point compared to at Week 1 (baseline, just before treatment commenced for flushing) ($p=0.017$) and at both the four-week and follow-up time points compared to at Week 1 for redness ($p=0.022$ and $p=0.021$, respectively) (Figure 2A). There was a reduction in the sensation of burning and stinging in the follow-up period ($p=0.032$) and, although the intensity of telangiectasia, papules/pustules, or itching was not statistically different, patients did report a decrease in each of these features at both the Week 4 and the follow-up phase (Figure 2B).

The treating practitioner reported an improvement in all signs and symptoms of rosacea, with significant effects noted in redness, telangiectasia, burning and stinging, and papules and pustules (Figure 2C). The treating practitioner also assessed additional rosacea signs and symptoms. Treatment did not significantly affect the presence of plaques, ocular manifestations, edema, or the presence of enlarged pores; however, it significantly

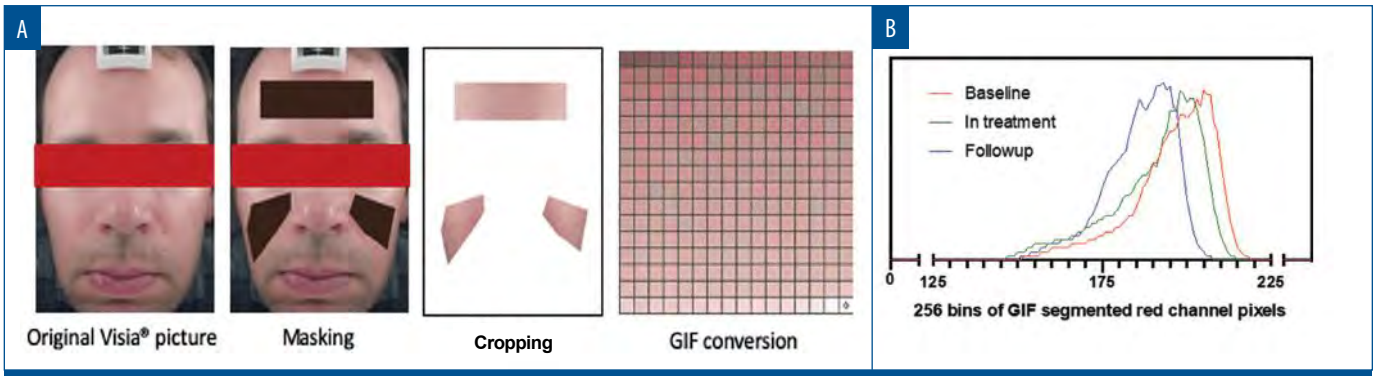

FIGURE 1. The Kleresca® biophotonic platform treatment decreased the erythematous reaction of rosacea. A) Preparation of images for advanced analysis; a predefined area, including the forehead and cheeks was applied to all VISIA® images. The masked area of the pictures was cropped and only the red channel of the RGB pictures was used. Subsequently, the red-channel pictures were transformed into a GIF file format for further analysis. B) A representative patient frequency distribution of the intensity of all red pixels in the masked GIF image. This distribution was calculated for all images per patient. The data were analyzed for the overall change in distribution and intensity of red pixels between the three time points. The combined patients showed a significant overall decrease in redness (N=9) ($p<0.001$).

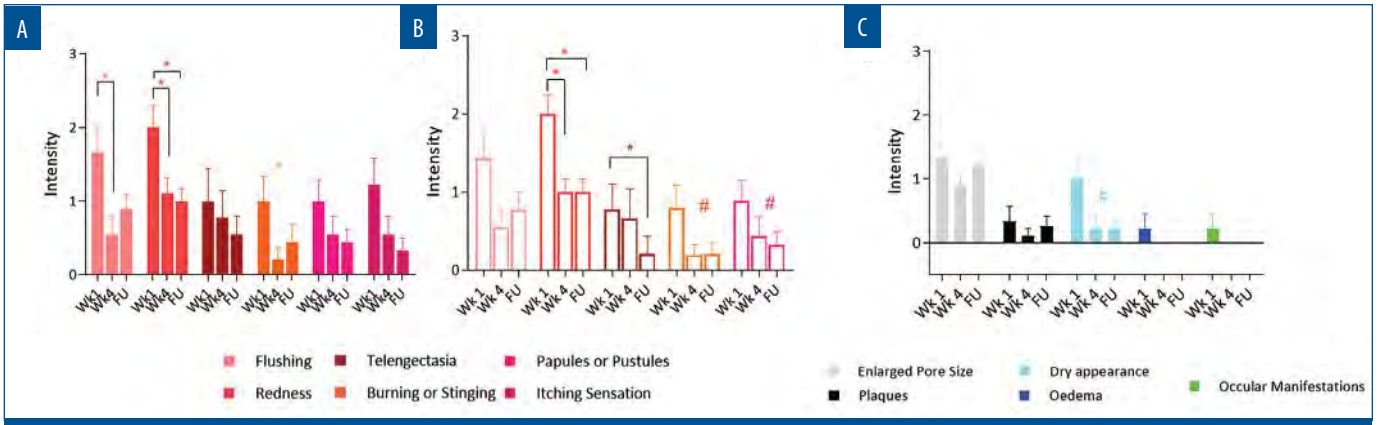

FIGURE 2. The Kleresca® biophotonic platform treatment improved the signs and symptoms of rosacea; A) group data presented as mean±standard error of the mean values for rosacea signs and symptoms of flushing, redness, telangiectasia, burning/stinging, papules or pustules, and itching sensation assessed by patients and; B) assessed by the treating practitioner. C) The treating practitioner also assessed the presence of enlarged pores, plaques, the presence of dry skin, edema, and ocular manifestations. Data were statistically compared with one-way analysis of variance and Tukey's *post-hoc* test. *$p<0.025$; #overall analysis of variance response, $p<0.05$

improved the appearance of dry skin ($p=0.048$) (Figure 2C).

Skin quality. Patients reported significant improvements in all manners of the skin's appearance. The presence of enlarged pores, the overall skin texture, and the overall skin appearance were all significantly improved ($p=0.004$, $p<0.0001$, and $p=0.0007$, respectively) (Figure 3A). These improvements were reported at both the four-week and follow-up time points (Figure 3A). However, the treating practitioner only noted improvements in the skin's appearance in the follow-up period ($p=0.024$ for skin texture and $p=0.049$ for overall skin appearance) (Figure 3A).

Effects of rosacea on participants. In response to the question, "how is your rosacea affecting you?," there was a significant improvement noted in the effect of rosacea among the participants ($p=0.0006$) (Figure 3B). This was observed at both the four-week time point ($p=0.019$), and the follow-up session relative to at Week 1 ($p=0.0005$) (Figure 3B). There was no difference in the effect of rosacea between Week 4 and the follow-up period (Figure 3B).

Patients' satisfaction and concerns about perceptions of others. Specific questions addressed how the patients were feeling about their condition before and after the four treatments. Patients were more satisfied with the appearance of their face in relation to rosacea and less worried that people will jump to conclusions (i.e., alcoholic or shy) based on their facial redness ($p=0.040$ and $p=0.002$, respectively) (Table 2). The treatment also affected the patients' concerns about the perceptions of others; patients disagreed more with the statements that they were less likely to be happy following treatment ($p=0.023$) (Table 2), that they were less likely to have a romantic partner ($p=0.030$), that they were less likely to be confident ($p=0.022$), and that they were more likely to be unhealthy ($p=0.040$) (Table 2).

Having completed the treatment, 80 percent of patients either agreed or strongly agreed that they would recommend the treatment to others and 60 percent of patients said they would repeat the treatment.

DISCUSSION

This study sought to evaluate the clinical efficacy along with the patient's and treating practitioner's perceptions of the biophotonic treatment. Questionnaires specifically addressed the impact of rosacea and its signs and symptoms on the patients and evaluated the

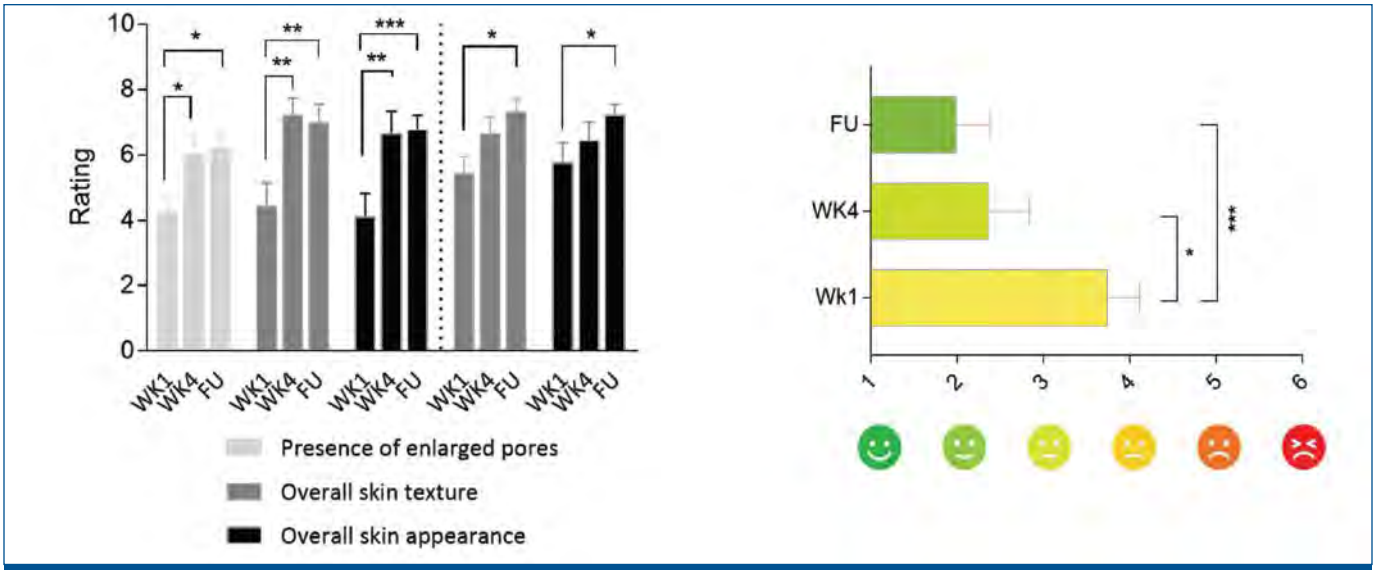

FIGURE 3. The Kleresca® biophotonic platform treatment improved patients' skin quality and had a positive effect on the impact of rosacea on patients; Group data presented as mean±standard error of the mean values for skin quality parameters, including A) the presence of enlarged pores, the overall skin quality, and the overall skin texture as assessed by the patients (left of the dashed line) and treating practitioner (right of the dashed line). B) The impact of rosacea on patients, comparing Week 1 to Week 4 and the follow-up period. Data were statistically compared with one-way analysis of variance and Tukey's post-hoc test; *$p<0.05$; **$p<0.025$; ***$p<0.0005$

TABLE 2. Patient satisfaction with facial appearance and concerns about others' perceptions based on their rosacea

PATIENT SURVEY STATEMENT	STATEMENT MEAN LIKERT SCALE (% AGREE OR STRONGLY AGREE)	
	BEFORE TREATMENT, MEAN ± SEM (%)	AFTER TREATMENT, MEAN ± SEM (%)
Patient satisfaction		
I am satisfied with the appearance of my face in relation to my rosacea	2.2±0.4 (22)	3.2±0.3 (45) *
I worry how people will react when they see my rosacea	3.6±0.4 (67)	3.0±0.4 (56)
Because of my rosacea I am uncomfortable in public	3.6±0.4 (67)	2.9±0.4 (44)
I feel rejected/discriminated against because of my rosacea	2.1±0.3 (0)	1.9±0.4 (11)
I feel rejected/discriminated against in the workplace because of my rosacea	1.8±0.3 (0)	1.8±0.3 (0)
I feel my rosacea is unattractive to others	4.2±0.2 (100)	3.4±0.3 (67)
Changes in my appearance due to my rosacea have affected my relationships	3±0.4 (44)	2.0±0.2 (0)
I worry that people jump to conclusions about me based on my facial redness (i.e. alcoholic or shy)	4.2±0.2 (89)	2.7±0.4 (33) *
I worry that people jump to conclusions about me based on my facial bumps or pimples (i.e. poor diet or hygiene)	3.1±0.5 (33)	2.7±0.4 (33)
I worry that, based on the appearance of my rosacea, people feel that:		
I am less likely to be intelligent	2.0±0.3 (0)	2.1±0.3 (0)
I am less likely to be successful	2.4±0.3 (11)	2.7±0.3 (22)
I am less likely to be confident	3.8±0.3 (78)	3.1±0.3 (33) *
I am more likely to be shy	4.0±0.2 (78)	3.8±0.3 (78)
I am more likely to be unhealthy	3.6±0.5 (67)	2.6±0.4 (22) *
I am less likely to have a romantic partner	3.6±0.3 (56)	2.9±0.3 (11) *
I am less likely to be happy	3.8±0.3 (78)	2.6±0.3 (22) *

SEM: standard error of the mean

Patient responses were reported using a five-point Likert scale (1=strongly disagree; 2=disagree; 3=neither agree nor disagree; 4=agree; 5=strongly agree). Questions adapted from Zeichner et al[10] were answered before the first treatment and following the final treatment session. Data were statistically compared by paired Student's t-test. * $p<0.05$; ** $p<0.01$

effects of treatment. The key findings were: 1) there was a significant reduction in the overall facial redness, most notable in the follow-up phase of the study; 2) the treatment had a positive effect on the impact of rosacea on the patients; 3) the treatment improved most signs and symptoms of rosacea, with notable effects in both flushing and redness; and 4) the overall appearance of the skin was improved during and maintained following treatment.

Rosacea is a complex condition; in addition to it having a multifactorial etiology, affected patients suffer from chronic cyclical episodes, including periods of exacerbation and remission, making it difficult to treat.[16] Here, we report a significant improvement in the redness of the skin during and following treatment. There is a lack of effective treatment options for this bothersome feature, described in the literature as an unmet need.[7,8] Indeed, patients had previously tried a range of topical and systemic therapies (e.g., ivermectin, azelaic acid, elidel cream, metronidazole, and doxycycline), with limited success. The clinical efficacy of the KBP inducing FLE has been reported in numerous clinical studies. This approach reduces inflammation and associated lesions in acne vulgaris[17,18]; targets the inflammatory and erythematous reaction common to rosacea subtypes 1, 2, and 3[14,15]; targets inflammation in granulomatous rosacea[19] and erlotinib-induced acneiform eruptions[20]; and improves the overall texture of the skin.[15,21,22] This study addressed the effect of a rosacea-specific chromophore-containing gel on the erythematous and inflammatory reactions of rosacea. The ability of FLE to successfully decrease the facial redness response, common across the continuum of rosacea subtypes,[11] offers a new therapeutic approach.

Recent work has focused on elucidating some of the key mechanisms underpinning the therapeutic effect of FLE. *In-vitro* work reports the capacity to modulate the inflammatory signature of key cutaneous cells and induce angiogenesis.[23] A consistent outcome of many photobiomodulation-inducing devices is the ability to modulate inflammation,[24] a known characteristic of many dermatological indications,[25] including rosacea.[26,27] The release of both interleukin-6 and tumour necrosis factor-α, two key proinflammatory cytokines, was reduced from human dermal fibroblasts and epidermal keratinocytes exposed to M1-like conditioned media and treated with FLE.[23] The ability of FLE to tune down this response might play a part in the resolution of redness observed in our patients, since an exaggerated immune response, including the production of proinflammatory cytokines and chemokines, plays a role in rosacea pathogenesis.[16,27] Additionally, in noninflamed conditions, FLE has been shown to encourage angiogenesis, an effect that might be considered as counterintuitive in rosacea at first. However, following the resolution of inflammation, the ability of FLE to induce healthy neovasculature, we reason, might assist in the distribution of blood, destress the skin, and help in the treatment of facial erythema.

In addition to the physical symptoms of rosacea, the condition poses a significant psychosocial burden for patients and has a negative impact on their QoL.[10,28] We sought to capture the impact of rosacea signs and symptoms on patients' emotional wellbeing, self-perceptions, and satisfaction before and following treatment.

Our questionnaires were designed so patients and the treating practitioner could rate the intensity of the common rosacea features and report how the treatment affected them. Improvements were reported in all rosacea signs and symptoms, with significant effects noted in flushing and redness from the patients' perspective, while the treating practitioner noted significant improvements not only in nontransient erythema, but also telangiectasias, burning and stinging, and the appearance of papules and pustules. Facial erythema is known to have a major negative impact on patients' self-perception, irrespective of whether they are suffering from ETR or PPR.[10] Interestingly, Moustafa et al[29] noted that new treatment options that can effectively target facial erythema might help to mitigate the negative psychological impact of rosacea. In addition to erythema, flushing has been noted as one of the key symptoms of rosacea linked to social anxiety common among patients with rosacea.[30] A very promising outcome of this study is the significant improvement in both flushing and redness self-reported by the participants after only three treatment sessions, which was maintained in the follow-up period.

Our patients' satisfaction with the treatment is most evident from the response to the question, "how is your rosacea affecting you?," which significantly improved during and following treatment.

Rosacea has a substantial negative impact on participants in many aspects of QoL, including: emotional well-being, self-perception, and functional limitations due to emotional problems.[10] From the assessment of participants' concerns about others' perceptions, at least 50 percent of patients agreed or strongly agreed that their happiness, relationships, health, confidence, and shyness were all affected by rosacea. The treatment significantly improved their concerns about happiness, relationships, and health. FLE significantly improved the patients' satisfaction with their facial appearance and decreased their concerns about other people jumping to conclusions about their facial redness.

In addition to the therapeutic portfolio of FLE in treating inflammatory skin conditions such as acne and rosacea,[14,15,17–20] it also has an aesthetic application, rejuvenating the skin and improving its overall appearance.[15,21] In typically healthy skin, FLE increased collagen production, reduced the appearance of visible pores, fine lines, and wrinkles.[21] Moreover, in a case report of PPR, along with a marked reduction in the inflammatory reaction of the skin, the KBP also improved the overall texture of the patient's large pore skin type.[15] Hence, in addition to its therapeutic efficacy, FLE offers an additional aesthetic benefit to patients. In the current study, this was captured by both the patients and the treating practitioner who assessed and rated the appearance of the skin. The patients noted significant improvements in all manners of their skin's appearance, including the presence of enlarged pores and the texture and overall appearance of the skin. Patients noted these improvements at both the four-week time point and follow-up assessment. While the treating practitioner also noted improvements in the skin's texture and overall appearance, these were significant in the follow-up session. It is noteworthy that the treating practitioner's initial assessment of the skin was more positive than the patient's assessment. However, both reported similar final endpoints. This divergence highlights the negative perception patients have about their own skin before any treatment and, for clinicians, the importance of speaking to patients and gaining their feedback throughout a treatment regimen.[8]

A minor limitation of the study is the single time point for the follow-up assessment.

While this ranged from 8 to 12 weeks across participants, it would be beneficial to have a longer follow-up period with several assessments due to the chronic relapsing and remitting features of the condition. It is noteworthy that, in a recent case study reporting the beneficial effects of FLE in the PPR and ETR components of granulomatous rosacea, there was no relapse in the condition at six months following treatment.[19]

CONCLUSION

We have shown the capability of the KBP to significantly reduce the inflammatory erythematous reaction, a major debilitating feature of rosacea. Further, patients and the treating practitioner reported an improvement in the many signs and symptoms of the condition and an improvement in the overall appearance and texture of the skin. Significant improvements were also noted in the patients' satisfaction with their skin and concerns about others' perceptions. Finally, following only three treatments, patients reported a significant improvement in how the condition was affecting them. The KBP utilising FLE can be considered a new treatment approach to rosacea, targeting the inflammatory erythematous reaction of the condition, improving the overall appearance of the skin, and positively affecting patients' psychological wellbeing.

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