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The Efficacy of Intense Pulsed Light Combined With Meibomian Gland Expression for the Treatment of Dry Eye Disease Due to Meibomian Gland Dysfunction: A Multicenter, Randomized Controlled Trial

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Objectives: To compare the efficacy of intense pulsed light (IPL) combined with Meibomian gland expression (MGX), and instant warm compresses combined with MGX, for treatment of dry eye disease (DED) due to meibomian gland dysfunction (MGD).

Methods: In a prospective, multicenter, interventional study, 120 subjects with DED due to MGD were randomized 1:1 to an IPL arm or a control arm. Each subject was treated 3 times at 3-week intervals. The primary outcome measure was the tear break up time (TBUT). Tear break up time and a few additional outcome measures were evaluated at the baseline and at 3 weeks after the last treatment.

Results: All outcome measures improved in both arms, but in general, the improvement was significantly larger in the IPL arm. Tear break up time increased by 2.3±1.9 and 0.5±1.4 sec, in the IPL and control arms respectively ($P<0.001$). SPEED was reduced by 38% and 22% in the IPL and control arms, respectively ($P<0.01$). Meibomian Gland Yielding Secretion Score was improved by 197% in the IPL arm and 96% in the control arm. Corneal fluorescein staining also decreased by 51% and 24% in the IPL and control arms respectively, but the differences between the two arms were not statistically significant ($P=0.61$). A composite score of lid margin abnormalities improved in both arms, but more in the IPL arm ($P<0.05$).

Conclusions: Intense pulsed light combined with MGX therapy was significantly more effective than instant warm compresses followed with MGX. This suggests that the IPL component has a genuine contribution to the improvement of signs and symptoms of DED.

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Dry eye disease (DED) is a chronic ocular surface disease (OSD), with severe impact on vision-related quality of life.[1] Depending on geography and populations, prevalence ranges from 5% to 50%, reaching up to 75% in one publication.[2] Most DED cases are caused by excessive evaporation of the tear film,[3] mainly due to obstructive meibomian gland dysfunction (MGD).[4,5] Meibomian gland dysfunction is characterized by inflammation, clogging, or terminal duct obstruction of the lipid-secreting meibomian glands within the eyelids. Impairment in the function of these glands leads to a deficiency in the lipid layer of the tear film, whose normal role is to protect the aqueous layer of the tear film and to prevent its evaporation. Destabilization of the tear film exposes the cornea and, eventually, triggers the development of DED symptoms.[5]

The high and rapidly growing incidence of DED pushes forward the need for finding novel therapeutic approaches and more efficient management techniques of this chronic condition. Recently, the Management and Therapy Subcommittee of the TFOS DEWS II recommended intense pulsed light (IPL) as a second step therapy after education, lid hygiene, and different types of ocular lubricants.[6] IPL technology consists of brief pulses of noncoherent light (400–1,200 nm), administered on to the surface of the skin. In 2005, Toyos et al[7] discovered that rosacea patients, treated with IPL in the periocular area, reported a remarkable improvement in their dry eye symptoms. A plausible explanation for this finding is that, since facial rosacea is strongly associated with MGD and blepharitis,[8] IPL treatment of rosacea could have eliminated abnormal telangiectasia in the periocular region, thereby removing a major source of inflammation to the eyelid sand, consequently, alleviating symptoms of MGD and dry eye.

Since the original publication of Toyos, a large number of studies have provided supportive evidence for the efficacy (and safety) of IPL therapy for patients with DED due to MGD. Many of these studies found that symptoms and a wide variety of DED/MGD signs improved in these patients, including tear break up time (TBUT), noninvasive breakup time (NIBUT), Schirmer test, presence of

inflammatory markers in the tear samples, lipid layer grade, lipid layer thickness, corneal fluorescein staining (CFS), meibum quality, meibum expressibility, and lid margin abnormalities.

So far, only two relevant randomized control trials (RCTs), in which randomization was per *subject*, were published. In one RCT, subjects were randomized to a series of IPL treatments in the study arm, or to a daily regimen of lid hygiene in the control arm.[9] Subjects in both arms improved in a variety of MGD signs, such as meibum quality, meibum expressibility, TBUT, and gland dropout. However, between the two arms there were no significant differences in these outcome measures, possibly because the study was under-powered. Despite its small sample size, the authors did find several anatomical differences between the two arms. Using confocal microscopy, the authors observed that the microstructure of meibomian glands, and the rate of inflammatory cells around the glands, improved in the study arm, but not in the control arm. In another RCT conducted by Arita and her group, subjects were randomized to a series of IPL followed by meibomian gland expression (MGX) in the study arm, or a series of monotherapy MGX in the control arm.[10] The authors reported a significant improvement of lipid layer thickness and CFS in the study arm, but not in the control arm. Noninvasive breakup time and TBUT improved in both arms, but significantly more in the study arm. Symptoms, however, similarly improved in both groups. One possible limitation of this study was the relatively long regimen of 8 treatment sessions, spaced at 3-week intervals (21 weeks in total, excluding the follow-up visits). If one wishes to infer from this study about the efficacy of IPL in a real-life situation, this could be a limitation: for practical reasons, subjects are more likely to sustain treatment from beginning to end if the schedule is shorter and there are less treatment sessions. Indeed, in all other studies of IPL for treatment of DED, the duration of treatment was between 3 or 4 treatment sessions spaced at 3- to 4-week intervals (6–12 weeks in total, excluding follow-up visits).

To demonstrate the contribution of IPL as a practical approach for treatment of DED due to MGD, additional well-designed RCTs are therefore much needed. The purpose of this current RCT was to answer this need and to provide further support for the efficacy of IPL in reducing signs and symptoms of DED.

METHODS

This multi-center study was performed in four sites in China. The study was approved by the respective ethics committees of these four sites. All study procedures adhered to the tenets of the Declaration of Helsinki. Before enrollment in the study, candidates signed an informed consent form. The study was registered in the Chinese Clinical Trial Registry (ChiCTR1800014787, http://www.chictr.org.cn).

Subjects

Subjects were recruited between November 2017 and April 2018. Inclusion criteria included male or female subjects over the age of 18; Fitzpatrick skin types I-IV; symptoms of DED (SPEED score of at least six points); bilateral evidence of meibomian gland obstruction; bilateral TBUT shorter than 10 sec; and bilateral evidence of corneal punctate staining or corneal lesions on CFS examination. For eyes with TBUT shorter than 5 sec, the CFS criterion was not applied. Excluded from the study were patients with contraindications to IPL (e.g., recent tanning in the treatment area, skin cancer or nervous paralysis in the treatment area, active ocular infection or allergies, acute or chronic ocular inflammation, recent ocular surgery, recent use of photosensitive drugs, background of migraines, background of head and neck radiotherapy, and history of chemotherapy), subjects with recent or current dry eye management (e.g., punctal plugs, eye drops excluding artificial tears, or recent facial IPL therapy), subjects with obvious scar or severe keratinization of the lid margin, pregnant/lactating women, and subjects with OSDs (e.g., ocular cicatricial pemphigoid, stevens-johnson syndrome and graft-versus-host disease).

Design

Subjects who passed all inclusion and exclusion criteria were randomized (1:1) to a control arm or an IPL arm. Randomization was implemented using an interactive web response system (IWRS).

Schedule

Baseline (BL) measurements were performed 0 to 14 days before the first treatment. Each subject was then treated 3 times at the clinic, at 3-week intervals. A follow-up examination (FU) was scheduled at 3 weeks after the third treatment. Subjects were allowed to advance or delay their scheduled visits by up to 3 days.

Treatment

Subjects in both arms were instructed to use artificial tears (Systane, Alcon, 5 mL) 3 times daily, during the entire duration of the study. There was at least a 60-min interval between eyedrops instillation and measurement of TBUT. All the bottles of Systane were recycled and checked by the investigator to make sure every patient used it. Every follow-up, the investigators would check the compliance by asking patients questions. All subjects were treated 3 times at the clinic, at 3-week intervals.

Subjects in the control arm were treated with conventional warm compress (WC) therapy in the hospital, consisting of a 20-min application of a moisture chamber eye mask (Shandong Zhushi Pharmaceutical, China). Warm compress was immediately followed by manual expression of the meibomian glands (MGX), which was performed by the ophthalmologist, with a forceps-shaped Arita meibomian gland compressor (Katena Products, Inc, Denville, NJ).

Subjects in the study arm were treated with a series of IPL pulses (M22 OPT; Lumenis, Israel). The fluence per pulse was 12 to 15 J/cm^2, depending on Fitzpatrick skin type. Before the IPL treatment, the patient's face was cleaned with a cosmetic face cleaner. During each treatment, the patients were asked to close both eyes, and eyelids were sealed with eye shields; a layer of ultrasound gel was applied to the treated skin. Before the IPL treatment, 1 to 2 test points were performed. It is recommended to start the test point on the lateral side of the tibia. Patients received a total of 14～16 pulses, with no more than 1 mm of overlapping. The treatment area includes the preauricular area from both sides to the nose below the eyes, and the forehead above the eyes.[9] The energy density of the forehead is appropriately lowered 1 to 2 J/cm^2. The irradiation site should be at least 3 mm from the lower lid margin. Usually, only 3 to 4 pulses are required from the preauricular area to the entire treatment area of the nose. The treatment was repeated one time. Intense pulsed light administration was immediately followed by MGX.

Clinical Outcomes

Clinical outcomes were estimated by the same examiners.

The primary outcome measure chosen for the study was TBUT. After instillation of fluorescein in the conjunctival sac with fluorescein sodium strips (Jingming New Technological

Development Co Ltd, Tianjin, China), the subject was asked to blink several times. Then, the tear film was observed under the slitlamp, using a cobalt blue filter to increase the visual contrast. For each eye, TBUT was evaluated three consecutive times, and the average of these three measurements was calculated and taken for the analysis. Tear break up time was measured at BL, at Tx2 (just before the second treatment), at Tx3 (just before the third treatment), and at FU (3 weeks after the third treatment).

Symptoms of DED were collected, per subject, with the self-evaluated Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire (Tear Science, Morrisville, VC). This validated questionnaire[11] asked the subject to grade the frequency and severity of four symptoms categories: (1) dryness, grittiness or scratchiness; (2) soreness or irritation; (3) burning or watering; and (4) eye fatigue. For each of these symptom categories, the subject subscored the frequency using a 4-point scale (0 = never, 1 = sometimes, 2 = often, 3 = constant), and subscored the severity using a 5-point scale (0 = none, 1 = tolerable, 2 = uncomfortable, 3 = bothersome, 4 = intolerable). The SPEED score was calculated as the sum of these eight subscores. A SPEED score ≥10 is widely accepted as indicating severe DED symptoms,[12] and a cut-off value around six is often used to distinguish between asymptomatic/mild and moderate/severe symptoms.[13] In the current study, we used a cutoff value of 6 as one of the inclusion criteria, and a cutoff value of 10 to estimate how many subjects improved from severe symptoms to nonsevere symptoms. SPEED score was collected at BL and FU.

The quality of the meibum was assessed by expressing the meibomian glands with the Meibomian Gland Evaluator (MGE; Tear Science, Inc, Morrisville, NC), a standardized instrument developed by Korb and Blackie,[14] and then evaluating the quality of meibomian secretions. MGE was applied on a total of 15 glands (5 nasal+5 central+5 temporal) along the lower eyelid. For each individual gland, the examiner subscored the quality of the expressed meibum using a four point-scale: 0 (no secretion), 1 (inspissated or toothpaste-like secretion), 2 (cloudy liquid secretion), or 3 (clear liquid secretion). The sum of these 15 subscores, ranging from 0 to 45, defined the Meibomian Gland Yielding Secretion Score (MGYSS). Meibomian Gland Yielding Secretion Score was evaluated at BL and FU.

Corneal staining was assessed using the method described in Ref. 15: immediately following TBUT measurement and taking advantage of the residual staining in the ocular surface, the examiner observed four anatomical quadrants of the cornea (temporal superior, temporal inferior, nasal superior, nasal inferior) under the slitlamp. Each quadrant was subscored using a 4-point scale: 0 (no staining), 1 (1–30 instances of punctate staining), 2 (>30 instances of punctate staining, without infused lesions or ulcers), or 3 (existence of infused lesions or ulcers). The sum of these four subscores, ranging from 0 to 12, defined the CFS score. The CFS score was evaluated at BL and FU.

A Composite Eyelid Score (CES) was compounded based on the presence or absence of five abnormal anatomical features of the eyelids: (1) hyperemia of anterior lid margin; (2) thicken lid margin; (3) rounded lid margin; (4) hyperkeratinization of the lid margin; and (5) telangiectasia around meibomian gland orifices. These five features were evaluated at BL and FU. Each feature was subscored 1 if the abnormality was present, or 0 otherwise. In the analysis, CES was calculated as the sum of these five subscores, thus ranging from 0 (all five features absent) to 5 (all five features present). At FU, the examiner used photos of the eyelids captured at BL to determine whether there was an improvement (+1), no change (0), or a deterioration (−1) for each of these features. The sum of these five subscores, ranging from −5 (if all five features deteriorated) to +5 (if all five features improved), was defined as the Change in CES (CCES).

Statistical Analysis

All statistical analyses were done with JMP 14.0.0 (SAS statistical software).

A minimal sample size of 47 patients per arm was calculated on the basis of an assumed mean TBUT difference of 2 sec between the control and IPL arms, for a 2-tailed test at an alpha level of 0.05 and a power of 80%. Assuming a drop-off rate of 20%, the total sample size was determined to be 120 patients (60 patients per arm).

Except for SPEED, which was collected per subject, all other outcome measures (TBUT, CFS, MGYSS, CES, and CCES) were collected per eye. In the analysis, one must consider the possibility of a significant intereye correlation within subjects. Figure 1 indicates that, indeed, the TBUT values of the two eyes of the same subject were highly correlated at BL. Because of the significant intereye correlation, eyes of the same subject could not be treated independently. Therefore, for each outcome measure collected per eye, all statistical analyses were performed on the "average eye," defined as the arithmetic average of the two eyes of a subject.

For continuous variables, descriptive statistics were expressed as mean (μ) ± SD (SD), mean (μ) ± SEM, and 95% confidence interval (CI) ($\mu \pm 2$ SEM). Within each arm, the absolute change of an outcome measure was calculated as the value of this outcome measure at FU minus its value at BL, averaged across all subjects in the arm. The statistical significance of this change was estimated with a paired (FU vs. BL) 2-tails *t* test. Result of this test was represented with a small "*P*" value, with the exact probability if $P>0.05$, or with one the following significance levels if otherwise: $P<0.05$ (–), $P< 0.01$ (**), $P<0.001$ (***), and $P<0.0001$ (****). The relative change of an outcome measure was calculated as the ratio of the absolute change and the value at BL, averaged across all subjects in the arm. Longitudinal analysis, relevant only for TBUT (because only TBUT had additional measurements taken between BL and FU), was performed using a multiple analysis of variance (ANOVA) (F-test with repeated measures).

Between arms, values at BL, values at FU, absolute changes, and relative changes were compared with unpaired two-tails t-test, assuming equal variance (ANOVA test). The result was represented with a large "*P*" value, with the exact probability if $P>0.05$, or with one of the following significance levels if otherwise: $P<0.05$ (*), $P< 0.01$ (**), $P<0.001$ (***), and $P<0.0001$ (****). Between the two arms, the difference in the absolute change (from BL to FU) was calculated with a linear regression model.

For categorical analyses, descriptive statistics were expressed as frequencies or proportions/percentages. The numbers of subjects in each category were compared with Chi-square tests. Odds ratios (ORs) were calculated with logistic regression. Dichotomization of an outcome measure below or above some meaningful cut-off value. This type of analysis was relevant only for TBUT and SPEED, for which meaningful threshold values could be defined according to the literature: for TBUT, a cut-off value of 5 sec was used to distinguish between moderate/severe TBUT (≤5 sec) and mild/normal TBUT (>5 sec). For SPEED, a cut-off value of 10

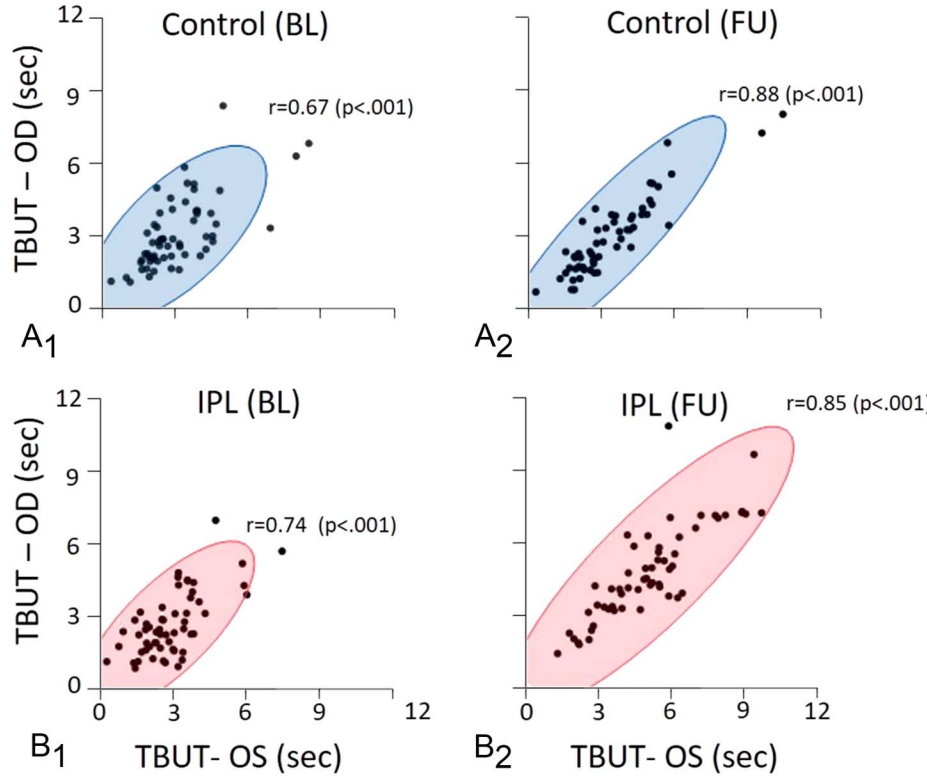

FIG. 1. Intereye correlation of tear breakup time (TBUT). Symbols: TBUT values of OD (right eye) and OS (left eye) in individual subjects; Shaded ellipsoids: 95% confidence intervals; r values: Pearson correlation coefficients; *P* values: probability of obtaining by chance a correlation with greater absolute value than the computed value (i.e., if no linear relationship exists between TBUT of OD and OS). A_1,A_2: Baseline and follow-up TBUT values in control subjects; B_1,B_2: Baseline and follow-sup TBUT values in IPL subjects. IPL, intense pulsed light.

was used to distinguish between severe (SPEED ≥10) and non-severe symptoms (SPEED <10).

Missing values, mostly because of a subject leaving the study early, were handled by two different methods: (1) by imputing the missing value using the Last Observation Carried Forward (LOCF) approach or (2) by excluding subjects who left the study early from the analysis. In general, these two types of analysis gave qualitatively similar results, because of a small number of missing values. In borderline cases, where the *P*-value was close to one of the statistical significance levels defined above, there were small qualitative differences. For simplicity, in the Results we present results only for analysis done on the imputed set. In cases where the analysis done on the imputed set was qualitatively different than the analysis done one the nonimputed set, we present both types of analysis.

RESULTS

One hundred and 20 subjects (120) subjects were enrolled and randomized to 60 subjects in the IPL arm and 60 subjects in the control arm. In the IPL arm, 1 subject left the study prematurely before Tx3. In the control arm, five subjects left prematurely: two before Tx2, 1 before Tx3, and two before FU.

Demographics and Baseline Values

Of the 120 enrolled subjects, 92 (77%) were women and 28 (23%) were men. The baseline characteristics of the study population is shown in Table 1. There was no statistically significant difference in gender proportions between the two arms: 20% (95% CI: 10% to 30%) were men in the control arm, and 27% (95% CI: 16% to 38%) were men in the IPL arm (P=0.39). The average age was 41.8±14.1 years in the control arm, and 42.4±14.2 years ($\mu\pm\sigma$) in the IPL arm (P=0.63). Fitzpatrick skin type range from II to IV in both arms, with an average of 3.1±0.5 for both (P=1). In the control arm, there were 5 (8%) subjects with skin type II, 43 (72%) subjects with skin type III, and 12 (20%) subjects with skin type IV. In the IPL arm, there were 9 (15%) subjects with skin type II, 35 (58%) subjects with skin type III, and 16 (27%) subjects with skin type IV. The distribution of skin types was similar in the two arms (P=0.28).

Between the two arms, there was no statistically significant difference in the baseline values of TBUT (P=0.53), SPEED (P=0.19), MGYSS (P=0.23), CSF (P=0.34), or CES (P=0.53) (Table 2).

Tear Breakup Time

Changes in the primary outcome measure TBUT are illustrated in Figures 1 and 2. There were no qualitative differences between analyses performed on the imputed set (120 pts) or on the non-imputed set (114 pts). Therefore, only the analysis performed on the imputed set is described below.

In Figure 1, we show the correlation of TBUT between OS (left eyes) and OD (right eyes). At BL, the Pearson correlation coefficient was 0.67 (P<0.001) for the control arm, and 0.74 (P<0.001) for the IPL arm. At FU, these intereye correlations increased to

TABLE 1. *Baseline Characteristics of the Study Population*

Baseline Characteristic	IPL Group (n=60)	WC Group (n=60)	*P*
Mean age (year)	42.4±14.2	41.8±14.1	0.63
Male, n (%)	16 (27%), 95% CI: 16%–38%	12 (20%), 95% CI: 10%–30%	0.39
Fitzpatrick type			0.28
II, n (%)	9 (15)	5 (8)	
III, n (%)	35 (58)	43 (72)	
IV, n (%)	16 (27)	12 (20)	

IPL, intense pulsed light; WC, warm compress.

0.88 and 0.85 for the control and IPL arms, respectively (both $P<0.001$). The increase in intereye correlation suggests that the improvement in TBUT was larger in the eye with the lower TBUT value at BL, such that at FU both eyes became more similar to each other.

Figure 2A shows a longitudinal analysis of TBUT in the two arms (multiple ANOVA, repeated measures test). TBUT gradually improved in both arms, but this increase was more pronounced in the IPL arm ($P<0.0001$), compared with the control arm ($P<0.05$). The separation between the two arms was apparent at FU, but not at earlier time points.

Figure 2B, C and Table 2 show the change of TBUT between BL and FU. In both arms, TBUT at FU was longer than TBUT at BL, but this improvement was more pronounced in the IPL arm. In the control arm, TBUT increased from 3.1±1.4 sec to 3.6±1.9 sec (μ±SD), the absolute change was 0.5±1.4 sec (μ±SD; $P<0.01$), and the relative change was +22%. In the IPL arm, TBUT increased from 3.0±1.4 sec to 5.3±2.3 sec (μ±SD), the absolute change was 2.3±1.9 sec (μ±SD; $P<0.0001$), and the relative change was +92%. Between the two arms, the *difference* in the absolute change was 1.8 sec higher in the IPL arm, compared with the control arm ($P<0.0001$).

The proportion of subjects with mild/normal TBUT (TBUT >5 sec) is illustrated in Figure 2D. In the control arm, this proportion modestly grew from 7% at BL to 15% at FU, but this increase was not statistically significant ($P=0.14$). In contrast, in the IPL arm this proportion grew from 8% at BL to 53% at FU ($P<0.0001$). The difference between the two arms was statistically significant ($P<0.0001$).

The percentage of subjects with moderate/severe TBUT at BL, who switched to mild/normal TBUT at FU, was also examined (not shown in the Figures or Tables): 11% (6 of 56) switched in the control arm, versus 51% (28 of 55) who switched in the IPL arm. The OR was 8.6 (95% CI: 3.2–23.4; $P<0.0001$). In other words, a subject in the IPL arm was about 9 times more likely to switch from moderate/severe TBUT at BL to mild/normal TBUT at FU, compared with a subject in the control arm.

Symptoms (SPEED)

Changes in symptoms (SPEED) are illustrated in Figure 3. In most cases, there were no qualitative differences between analyses done on the imputed set or on the nonimputed set, and therefore we usually describe the analysis performed on the imputed set only. An exception is the proportion of subjects who significantly improved, where there were small qualitative differences between the imputed and the non-imputed sets. For this case only, we describe the results of both analyses.

Figure 3 and Table 2 show the SPEED scores at BL and FU. In the control arm, the SPEED score decreased from 14.1±4.9 at BL to 10.7±4.7 (μ±SD) at FU (N=60; $P<0.0001$); In the IPL arm, the SPEED score decreased from 15.2±4.7 at BL to 9.2±4.8 (μ±SD) at FU (N=60; $P<0.0001$). Note that in the IPL arm, but not in the control arm, the average SPEED score at FU decreased below the threshold accepted as cutoff between severe and non-severe symptoms (dashed horizontal line in Fig. 3A). The absolute change of SPEED score was −3.4±4.7 (μ±SD) and −6.1±5.1 (μ±SD) for the control and IPL arms, respectively (Table 2), and this difference between the two arms was statistically significant ($P<0.01$). The relative change was −22% for the control arm, and −38% for the IPL arm, and this difference was also statistically significant (Fig. 3B, $P<0.01$).

In Figure 3C, we show the change in the proportion of subjects with severe symptoms. As explained in Methods, we used a cut-off value of 10 to separate between severe and nonsevere symptoms. In both arms, the percentage of subjects with severe symptoms decreased: from 80% at BL to 55% at FU in the control arm (N=60; $P<0.01$), and from 90% at BL to 40% at FU in the IPL arm (N=60; $P<0.0001$). There was a trend toward more subjects switching from severe to nonsevere symptoms in the IPL arm, compared with the control arm ($P=0.07$): 18 of 48 (38%) switched in the control arm, compared to 30 of 54 (56%) who switched in the IPL arm. The OR was 2.1 (95% CI: 0.9–4.6; $P=0.07$).

Meibomian Gland Yielding Secretion Score

Changes in MGYSS are presented in Figure 4A and Table 2. In most analyzes, there were no qualitative differences between the imputed set and the non-imputed set. Therefore, we usually describe the analyzes performed on the imputed set only. Where the analyzes done on the imputed set and non-imputed set gave qualitatively different results, we present both.

Meibomian Gland Yielding Secretion Score significantly improved in both arms, with the improvement more pronounced in the IPL arm compared to the Control arm: MGYSS increased from 5.3±3.3 to 8.7±5.9 (μ±SD) in the Control arm (N=60; $P<0.0001$), and from 4.6±3.3 to 10.8±6.8 (μ±SD) in the IPL arm (N=60; $P<0.0001$). The Absolute Change of MGYSS was 3.4±4.8 (μ±SD) and 6.2±6.0(μ±SD) in the Control and IPL arms, respectively. A difference of +2.9 between the two arms was statistically significant in both the imputed set ($P< 0.01$) and the non-imputed set ($P<0.05$). Relative change was 87% in the Control arm, and 193% in the IPL arm. Here as well, the statistical significance of this difference was qualitatively different in the imputed set ($P<0.05$), compared to the non-imputed set ($P=0.06$).

TABLE 2. *Continuous Analysis of Outcome Measures.*

Outcome Measure (Min to Max)	Arm	Baseline (BL)		Follow-Up (FU)		Absolute Change (FU-BL)			Rel. Change (FU-BL)/BL
		μ±SD (95% CI)	Median	μ±SD (95% CI)	Median	μ±SD (95% CI)	Median	FU vs. BL (*P*)	%
TBUT (sec) (0 to no limit)	IPL (N=60)	3.0±1.4 (2.6–3.3)	2.7	5.3±2.3 (4.7–5.9)	5.1	2.3±1.9 (1.8 to 2.8)	2.1	*d*	92
	Control (N=60)	3.1±1.4 (2.8–3.5)	2.8	3.6±1.9 (3.1–4.1)	3.2	0.5±1.4 (0.1 to 0.8)	0.4	*b*	22
	IPLs vs. Control (*P*-value)	0.53		*d*		*d*		—	*d*
SPEED (0–28)	IPL (N=60)	15.2±4.7 (14–16.4)	15	9.2±4.8 (7.9–10.4)	8	−6.1±5.1 (−7.4 to −4.8)	−6	*d*	−38
	Control (N=60)	14.1±4.9 (12.8–15.3)	13.5	10.7±4.7 (9.5–11.9)	10	−3.4±4.7 (−4.6 to −2.2)	−3	*d*	−22
	IPLs vs. Control (*P*-value)	0.19		0.08		*b*		—	*b*
MGYSS (imputed set) (0–45)	IPL (N=60)	4.6±3.3 (3.7–5.4)	4.3	10.8±6.8 (9.0–12.6)	8.8	6.2±6.0 (4.7 to 7.8)	5.5	*d*	193
	Control (N=60)	5.3±3.3 (4.8–5.8)	4.8	8.7±5.9 (8.1–9.3)	8	3.4±4.8 (2.8 to 4.0)	2.3	*d*	87
	IPLs vs. Control (*P*-value)	0.22		0.07		*b*		—	*a*
MGYSS (nonimputed set) (0–45)	IPL (N=59)	4.6±3.4 (3.7–5.4)	4.5	10.9±6.8 (9.2–12.7)	9	6.3±6.0 (4.8 to 7.9)	5.5	*d*	197
	Control (N=55)	5.4±3.4 (4.5–6.3)	5	9.1±6.0 (−4 to 26.5)	8.5	3.7±4.9 (2.4 to 5.0)	3	*d*	96
	IPLs vs. Control (*P*-value)	0.18		0.13		*a*		—	0.06
CFS (0–12)	IPL (N=60)	1.5±1.7 (1.1–1.9)	1	0.9±1.5 (0.5–1.2)	0	−0.6±1.0 (−0.9 to −0.4)	−0.5	*d*	−51
	Control (N=60)	1.8±2.0 (1.3–2.3)	1.5	1.0±1.5 (0.6–1.4)	0.5	−0.8±1.7 (−1.3 to −0.4)	0	*c*	−44
	IPLs vs. Control (*P*-value)	0.34		0.58		0.49		—	0.61
CES (composite eyelid score) (0–5)	IPL (N=60)	2.2±1.8 (1.8–2.7)	2	2.0±1.9 (1.5–2.5)	1.8	−0.3±0.5 (−0.4 to −0.1)	0	*c*	−24
	Control (N=60)	2.0±1.8 (1.5–2.5)	1	1.9±1.9 (1.4–2.3)	1	−0.2±0.4 (−0.3 to −0.1)	0	*c*	−17
	IPLs vs. Control (*P*-value)	0.53		0.72		0.31		—	0.39
CCES (change of CES) (−5 to 5)	IPL (N=60)	—		—		1.4 ±1.1 (1.1–1.7)	1	—	—
	Control (N=60)	—		—		0.9 ±1.1 (0.6–1.2)	0.75	—	—
	IPLs vs. Control (*P*-value)	—		—		*a*		—	—

Except where noted, results describe the analysis performed on the imputed set, where missing values were completed with a Last Observation Carried Forward (LOCF) approach.

Statistical significance levels:

[a] *P* or $P<0.05$.

[b] *P* or $P<0.01$.

[c] *P* or $P<0.001$.

[d] *P* or $P<0.0001$.

CFS, corneal fluorescein staining score; CES, composite eyelid score; CCES, change in composite eyelid score; MGYSS, meibomian gland yielding secretion score; SPEED, standardized patient evaluation of eye dryness score; TBUT, tear breakup time.

Corneal Fluorescein Staining

Changes in CFS are illustrated in Figure 4B and Table 2. There were no qualitative differences between analyzes performed on the imputed set and the non-imputed set. Therefore, only analyzes performed on the imputed set are described.

Corneal fluorescein staining improved in both arms, but there was no difference between the two arms: CFS decreased from 1.8±2.0 to 1.0±1.5 (μ±SD) in the Control arm (N=60; $P<0.001$), and from 1.5±1.7 to 0.9±1.5 (μ±SD) in the IPL arm (N=60; $P<0.0001$). The Absolute Change was −0.6±1.0 (μ±SD) and −0.8±1.7 (μ±SD) for the Control arm and IPL arm, respectively. The difference between the two arms, +0.18, was not statistically significant ($P=0.49$). The Relative Change was −44% for the Control arm, and −51% for the IPL arm ($P=0.61$).

Composite Eyelid Score and Change of Compound Eyelid Score

The CES summarized the existence or absence of five abnormal features of the eyelids: lid margin hyperemia of

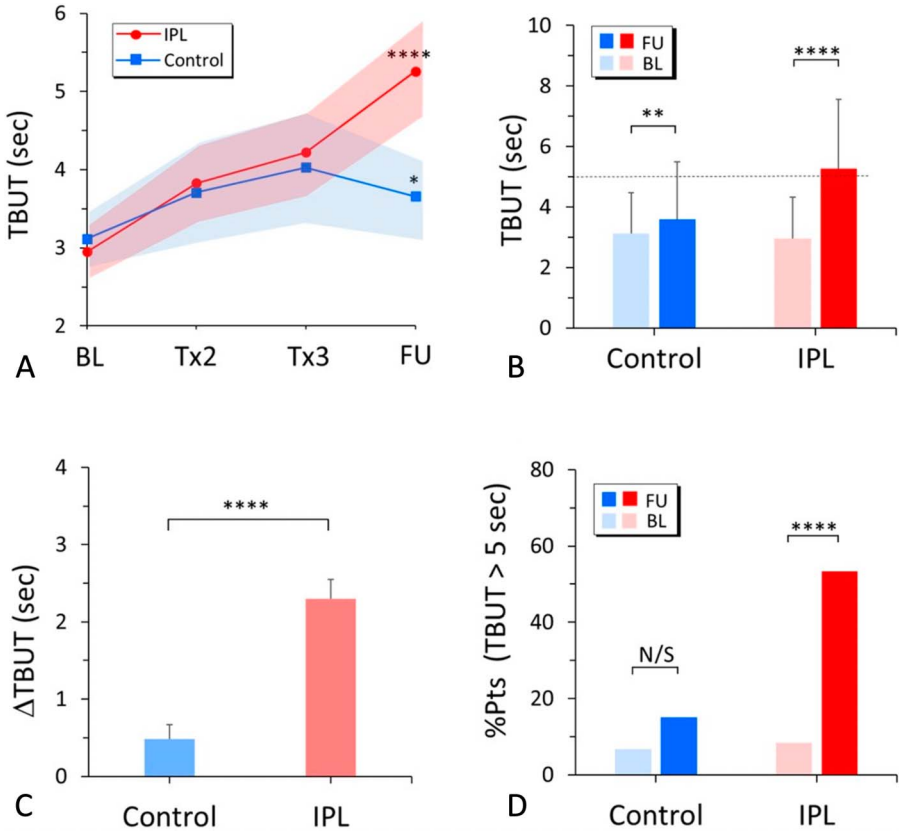

FIG. 2. Change in tear break up time (TBUT). For each subject, TBUT was defined as the arithmetic mean TBUTs in the two eyes. (A) Longitudinal analysis of TBUT, for control subjects (blue squares) and IPL subjects (red circles) at BL, Tx2, Tx3, and FU; Dashed areas: respective 95% confidence intervals; ****$P<0.0001$, *$P<0.05$. (B) TBUT at BL (pale colors) and FU (vivid colors), for control subjects (blue bars) and IPL subjects (red bars); error bars: SD; ****$P<0.0001$, **$P<0.01$; dashed horizontal line: cutoff value which distinguishes between moderate/severe TBUT and mild/normal TBUT (used in D). (C) Change of TBUT from BL to FU, for control subjects (blue bar) and IPL subjects (red bar); error bars: SEM; ****$P<0.0001$. (D) Percentage of pts with subclinical or normal TBUT (>5 sec) at BL (pale colors) and FU (vivid colors), for control subjects (blue bars) and IPL subjects (red bars); ****$P<0.0001$; N/S, nonsignificant; IPL, intense pulsed light.

anterior lid margin, thicken lid margin, rounded lid margin, hyperkeratinization of lid margin, and telangiectasia around meibomian gland orifices. The change of CES (CCES) reflected the change (improvement=+1/no change=0/deterioration=−1) in these five abnormal features of the eyelids, as assessed by comparing photos of the eyelids at BL and the appearance of eyelids at FU under the slitlamp.

The average changes of CES in the two arms are illustrated in Figure 4C and Table 2. Composite Eyelid Score improved in both arms, with no significant difference between the two arms: CES decreased from 2.0±1.8 to 1.5±2.5 (μ±SD) in the Control arm ($P<0.001$), and from 2.2±1.8 to 2.0±1.9 (μ±SD) in the IPL arm ($P<0.001$), respectively (Table 2). The absolute change was −0.2±0.4 (μ±SD) and −0.3±0.5 (μ±SD) in the control arm and IPL arm respectively, and the difference was not statistically significant ($P=0.31$). The relative change was −17% in the control arm and −24% in the IPL arm, and here as well the difference was not statistically significant ($P=0.39$).

Change of CES, however, was 0.9±1.1 (μ±SD) in the control arm, and 1.4±1.1 (μ±SD) in the IPL arm, and the difference between the two arms was statistically significant ($P<0.05$; Table 2).

Adverse Events

There were no changes in intra-ocular pressure, best-corrected visual acuity, or anterior segment inflammation in either group (not shown). In the IPL arm, there were no adverse events related to the device or the procedure. In the control group, one patient developed lower eyelid edema during the study and had to stop participation in the study.

DISCUSSION

So far, there were only two RCTs who examined the efficacy of IPL for treatment of evaporative DED secondary to MGD. One of these RCTs did not find a significant difference between subjects treated with IPL or subjects treated with lid hygiene, perhaps because the study was under-powered.[9] An interesting exception was a remarkable improvement in glandular morphology and rate of inflammatory cells in the IPL arm, and not in the control arm. The second study, conducted by Arita et al,[10] showed significant differences between subjects treated with IPL combined with MGX and MGX alone, including differences of 2.4 sec and 3.3 sec in the change of TBUT after 24 weeks and 32 weeks, respectively.

In our study, subjects were randomized to IPL+MGX (the IPL arm) and warm compresses+MGX (the control arm). Each subject was treated 3 times at 3 weeks intervals, and the outcome measures were evaluated at 12 weeks after the baseline. We found that subjects in both arms improved in symptoms (SPEED) and a variety of DED signs, but in general the improvement in the IPL arm was significantly more pronounced. In particular, our primary outcome measure TBUT increased by 0.5 sec in the control arm, compared with an increase of 2.3 sec in the IPL arm. The difference between the two arms was about 1.8 sec. Although the difference of 1.8 sec between the 2 arms was a bit smaller than the difference found by the group of Arita (2.3 sec after 24 weeks and 3.4 sec after 32

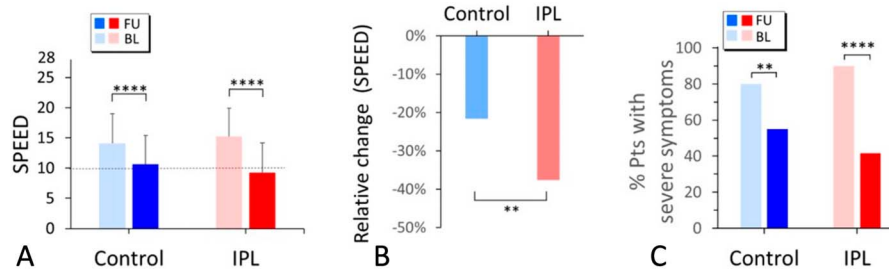

FIG. 3. Change in symptoms. (A) SPEED scores at BL (pale colors) and FU (vivid colors), in the control subjects (blue bars) and IPL subjects (red bars). Horizontal dashed line: cutoff value which distinguishes between severe symptoms and nonsevere symptoms; Error bars: SD; ****$P<0.0001$. (B) Change of SPEED score from BL to FU, for control subjects (blue bar) and IPL subjects (red bar); ****$P<0.0001$. (C) Percentage of pts with severe symptoms at BL (pale colors) and FU (vivid colors), for control subjects (blue bars) and IPL subjects (red bars); ****$P<0.0001$, **$P<0.005$. IPL, intense pulsed light.

weeks), one should note that the number of treatment sessions in our study was only 3, compared with eight treatment sessions in the study of Arita. In any case, we argue that a difference of 1.8 sec is still clinically meaningful, and this for several reasons: although there is no formal definition of the minimal clinically important difference (MCID) for TBUT, there are various indications in the literature that a difference around 2 sec is considered to be clinically meaningful. For example, the diagnosis subcommittee on the International Workshop on MGD proposed that TBUT ranges of 1 to 3 sec, 3 to 5 sec, and 5 to 7 sec indicate moderate, mild, and minimal severity levels, respectively.[16] Note that the difference between the midpoints of these consecutive ranges is 2 sec. Another indirect indication can be inferred from different therapies which were recently approved by internationally recognized regulatory agencies, such as Lipiflow (a thermal-pulsation device) which was FDA-cleared based on a TBUT improvement of 1.9 sec,[17] or Lifitegrast 5% (Xiidra) which was FDA-approved based on improvement in symptoms but also showed a TBUT improvement of 1.9 sec.[18]

Another interesting result was that subjects in the IPL arm were more likely to improve in their severity levels, compared with subjects in the control arm. For example, IPL subjects were 9 times more likely to switch from moderate/severe TBUT (<5 sec) to mild/normal TBUT (≥5 sec), compared with control subjects. Similar results were obtained for other outcome measures, including symptoms (SPEED), MGYSS, and CCES. In all these outcome measures, subjects in both arms improved, but the improvement was more pronounced in IPL subjects, compared with control subjects. An exception was CFS, which improved in both arms but with no significant difference between the two arms.

There were several limitations in our study: (1) Because of the nature of the study, the subjects could not be blinded to the allocation and were aware of the type of treatment they were receiving. The examiners who measured the outcome measures were not masked to the allocation. These could unconsciously bias the measurements of outcome measures. (2) In the IPL arm, the treatment consisted of IPL immediately followed by MGX. The improvement in symptoms and signs of DED probably results from the combination of these two procedures, but it is not clear what the relative contribution of each is. In our design of the study, an implicit assumption was made that the contribution of MGX in the IPL arm should be similar to the contribution of MGX in the control arm, and therefore the effect of MGX in the two arms should mostly cancel out, such that any difference between the two arms could be attributed to the difference between IPL and without IPL. The clinical recommendations for warm compresses would be daily application. So, the warm compresses here are just an assistant for MGX. However, the interaction between IPL and MGX on one hand, or warm compresses and MGX on the other hand, may be nonlinear and complex. Thus, there is a need to revisit or verify this assumption. Because IPL may be costly when performed in some centers, it is relevant to know whether persistent eyelid warming at home followed by WC/MGX can achieve similar outcomes as IPL/MGX. In future studies, it will be useful to compare monotherapy IPL with monotherapy of clinical warm compresses alone (or monotherapy of other types of active control, such as MGX). (3) The population of the study was predominantly Han Chinese. A similar study done in a population of different ethnicity may give different results. For example, in our study most subjects (88%) showed Fitzpatrick skin type III or IV, representing the skin distribution in this part of the world. However, the skin distribution in North Europe or North America, is different: most subjects in these countries have lighter skin type, mostly Fitzpatrick skin type II or III. Because darker skin types contain more

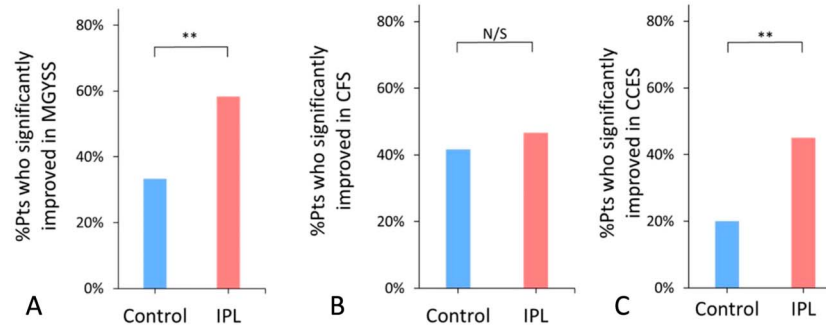

FIG. 4. Percentage of subjects who significantly improved in secondary outcome measures. Significant improvement of an outcome measure was arbitrarily defined as a change (from BL to FU) which exceeded the median change in the entire sample. (A) Percentage of subjects for whom MGYSS significantly improved (i.e., increased above +3.5, the median change of MGYSS in the entire sample); **$P<0.01$. (B) Percentage of subjects for whom CFS significantly improved (i.e., decreased below −0.5, the median change of CFS in the entire sample); N/S: nonsignificant. (C) Percentage of subjects for whom the change in the Compound Eyelid Score (CCES) was significantly high (i.e., above the median value of CCES in the entire sample); **$P<0.01$. CFS, corneal fluorescein staining.

melanin, for safety reasons there is an inverse relationship between the fluence used and the skin type: in darker skin types, IPL is administered with less fluence. The fluence used could affect the efficacy of IPL, although the exact relationship is not fully understood. Similar studies with other populations are therefore needed to extend our conclusions to the general case. It is therefore not unreasonable to assume that similar results would have been obtained in a different population with a different skin type distribution. (4) Another limitation was in the choice of TBUT as the primary outcome measure. Tear break up time is widely accepted as an outcome measure in many studies of DED, but this outcome measure is problematic for several reasons[19]: the sensitivity/specificity of this test is moderate, the results depend on the volume of dye (fluorescein) instilled in the eye, and in addition, the test is highly dependent of subjective assessment by the observer. Consequently, TBUT is variable across different examiners and even variable within the same examiner. In our study, each TBUT value used in the analysis was the average of three consecutive measurements of TBUT. Although this averaging method certainly reduced the variability in TBUT measurements, a more reliable and objective primary outcome measure (e.g., NI-BUT), may be a good alternative to examine in future studies. (5) Finally, there was an imbalance in the number of subjects who left the study early: five subjects in the control arm, versus 1 subject in the IPL arm. Because missing values were handled by imputation using the LOCF approach, in principle this imbalance could have somewhat favored the IPL arm. We therefore repeated all statistical analyses using a different method of handling missing values, namely excluding from the analysis subjects who left the study early. We found that, in general, there were no qualitative differences when missing values were handled by these two different methods-because of the fact that the number of missing values was small. An exception was in the proportion of subjects who significantly improved in SPEED in the IPL arm, compared with the control arm. When missing values were imputed, the difference (57% in the IPL arm versus 38% in the control arm) was statistically significant ($P<0.05$). This statistical significance was lost when missing values were handled by excluding subjects with missing values from the analysis, albeit there was a strong trend in the same direction ($P=0.09$). We conclude that a bias resulting from handling missing values by imputation was, if any, small and not significant for the overall conclusions.

Despite the promising results of this study and previous works, the mechanism of action is not fully understood.[20] One possibility is that IPL destroys Demodex mites on the skin, thereby reducing the bacterial load onto the eyelids and decreasing blepharitis and inflammation of the ocular surface.[21,22] Another possibility is that IPL acts by thrombosis of abnormal blood vessels (telangiectasia) in the periorbital area, thus preventing the release of inflammatory mediators by these abnormal vessels,[23] which could otherwise easily propagate to the eyelids via the orbital vasculature. It was also suggested that IPL activate fibroblasts and enhance collagen production, up-regulate the expression of anti-inflammatory agents, down-regulate pro-inflammatory agents, or modulates the production or reactive oxidative species.[21] Currently, there is no good understanding how these different mechanisms interact to reduce signs and symptoms of dry eye. A better understanding could be useful to optimize or even personalize the settings of IPL, thus further increasing its benefits for DED patients.

To conclude, our results indicate that IPL combined with MGX is a promising therapeutic approach for patients with DED due to MGD, and that the contribution of IPL is genuine and not merely a placebo effect. However, it is not clear what is the relative contribution of IPL in the overall treatment, which includes also MGX. Future randomized controlled trials are needed to shed more light on this issue. In addition, preclinical studies are needed to elucidate the mechanism of action, and perhaps further increase the benefits of this therapeutic approach.

REFERENCES

1. Li M, Gong L, Chapin WJ, et al. Assessment of vision-related quality of life in dry eye patients. *Invest Ophthalmol Vis Sci* 2012;53:5722–5727.
2. Nelson J, Craig J, Akpek E, et al. TFOS DEWS II introduction. *Ocul Surf* 2017;15:269–275.
3. Lemp M, Crews L, Bron A, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort. *Cornea* 2012;27: 472–478.
4. Mathers W. Ocular evaporation in meibomian gland dysfunction and dry eye. *Ophthalmology* 1993;100:347–351.
5. Nelson J, Shimazaki J, Benitez-del-Castillo J, et al. The international workshop on meibomian gland dysfunction: Report of the definition and classification subcommittee. *Invest Ophthalm Vis Sci* 2011;52:1930–1937.
6. Jones L, Downie L, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf* 2017;15:575–628.
7. Toyos R, Buffa C, Youngerman S. Case report- Dry–eye symptoms improve with intense pulsed light treatment. *EyeWorld* 2005;33:41–46.
8. Viso E, Rodríguez-Ares MD, Oubiña B, et al. Prevalence of asymptomatic and symptomatic meibomian gland dysfunction in the general population of Spain. *IOVS* 2012;53:2601–2606.
9. Yin Y, Liu N, Gong L, et al. Changes in the meibomian gland after exposure to intense pulsed light in meibomian gland dysfunction (MGD) patients. *Curr Eye Res* 2018;43:308–313.
10. Arita R, Fukuoka S, Morishige N. Therapeutic efficacy of intense pulsed light in patients with refractory meibomian gland dysfunction. *Ocul Surf* 2019;17:104–110.
11. Ngo W, Situ P, Keir N, et al. Psychometric properties and validation of the standard patient evaluation of eye dryness questionnaire. *Cornea* 2013;32: 1204–1210.
12. Blackie C, Solomon J, Scaffidi R, et al. The relationship between dry eye symptoms and lipid layer thickness. *Cornea* 2009;28:789–794.
13. Asiedu K, Kyei S, Mensah S, et al. Ocular surface disease index (OSDI) versus the standard patient evaluation of eye dryness (SPEED): A study of a nonclinical sample. *Cornea* 2016;35:175–180.
14. Korb D, Blackie C. Meibomian gland diagnostic expressibility: Correlation with dry eye symptoms and gland location. *Cornea* 2008;27:1142–1147.
15. Experts' consensus about clinical diagnosis and treatment. *Chin J Ophthalmol* 2013;49:73–75.
16. Tomlinson A, Korb D, Amano S, et al. The international workshop on meibomian gland dysfunction: Report of the diagnosis subcommittee. *IOVS* 2011;52:2006–2049.
17. Lane S, DuBiner H, Epstein R, et al. A new system, the LipiFlow, for the treatment of meibomian gland dysfunction. *Cornea* 2012;31:396–404.
18. Tong A, Passi S, Gupta P. Clinical outcomes of Lifitegrast 5% ophthalmic solution in the treatment of dry eye disease. *Eye Contact Lens* 2020; 46(Suppl 1):S20–S24.
19. Wolffsohn J, Arita R, Chalmers R, et al. TFOS DEWS II diagnostic methodology report. *Ocul Surf* 2017;15:539–574.
20. Dell S. Intense pulsed light for evaporative dry eye disease. *Clin Ophthalmol* 2017;11:1167–1173.
21. Prieto V, Sadick N, Lloreta J, et al. Effects of intense pulsed light on sun-damaged human skin, routine, and ultrastructural analysis. *Lasers Surg Med* 2002;30:82–85.
22. Zhang X, Song N, Gong L. Therapeutic effect on intense pulsed light on ocular demodicosis. *Curr Eye Res* 2019;44:250–256.
23. Schroeter C, Haaf-von BS, Neumann H. Effective treatment of rosacea using intense pulsed light systems. *Dermatol Surg* 2005;31:1285–1289.

