STUDY PROTOCOL

Official title: Combination of 0.09% cyclosporine and IPL therapy for the treatment of dry eye disease in symptomatic contact lens wearers: a sham-controlled randomized clinical trial

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NCT number : not assigned yet

Document date : April 22nd, 2024

INTRODUCTION

Background and rationale

Dry eye disease is a complex and multifactorial pathology in which the tear film is compromised. Inflammation and changes to the tear film (instability and hyperosmolarity) are central to this condition[1]. Dry eye disease is very common, with an estimated global prevalence of 11.59%[2] although some analyses conclude to 50% of some populations suffering from dry eye[3]. The condition has been traditionally classified in two subtypes: aqueous tear deficiency (secondary to a deficit of production by the lacrimal gland) and evaporative disease (secondary to a deficit of the lipid layer of the tear film), but research has shown that more than 80% of individuals with dry eye have mixed or predominantly evaporative dry eye disease and that, when the condition progresses, almost all patients present characteristics of both subtypes[4]. Hence, this classification has lost of its importance in the new approach to the disease[1]. Meibomian gland dysfunction (MGD) is one of the conditions that is most frequently associated with dry eye disease. It is the source of changes both in quantity and quality to the meibum that is released on the ocular surface and leads to evaporative dry eye as well as alterations of the ocular surface[5]. The prevalence of MGD has been recently computed between 21.2% and 29.5% in subjects of African and Caucasian race and higher among Arabs, Hispanics[6] and Asians[7]. Many risk factors exist for dry eye disease and MGD, including age and usage of contact lens[8].

Soft contact lenses are used by hundreds of millions of people to correct myopia, hyperopia, astigmatism and presbyopia[9]. The wear of contact lens, however, has the potential to create or worsen dry eye signs and symptoms[10]. Despite recent technological breakthroughs that have led to more sophisticated lens material, a large number of contact lens wearers still suffer from dry eye. A comparative study has found that 39% of North-American wearers can be categorized as symptomatic of contact lens dry eye[11] and the proportion of uncomfortable users increases with age[12]. A soft contact lens that is placed on the ocular surface disturbs the normal homeostasis of the tear film by splitting it in two compartments[13]. Contact lens wear can increase evaporative dry eye[14] by weakening the lipid layer, which leads to decreased stability[10] of the tear film and increased evaporation[15]. It also contributes to aqueous dry eye etiology[14] by reducing the tear volume[16]. The wear of contact lens has also been shown to have a damaging effect on meibomian glands[17, 18] and, in some cases, on the conjunctival goblet cells[8]. Arguments also support the role of contact lens in the inflammation of the ocular surface[19, 20], even in asymptomatic patients[21]. Thus, dry eye disease associated with contact lens wear is a complex condition that implies many different mechanisms.

Cyclosporine A is a peptide produced by a fungus that has been used systemically for decades for its potent immunomodulatory effects[22]. Usage for dry eye disease in a topical 0.05% oil-based formulation has been common since the early 2000s[23]. On the ocular surface, cyclosporine acts by inhibiting calcineurin, which subsequently blocks the activation of T cells and prevents the release of cytokines, therefore reducing inflammation[22]. It has been shown to increase tear volume, goblet cell density and to reduce surface staining as well as symptoms in dry eye patients[24-27]. Divergent results

have been observed on contact lens wearers[28, 29], although one study has found an amplified effect on contact lens wearers symptomatic of dry eye when combining essential fatty acid supplements with topical cyclosporine[30]. Despite having been shown useful in the management of dry eye disease, the oil-based formulation is considered having a low bioavailability[31]. A new cyclosporine eyedrop has been approved in Canada and the USA in the recent past years and is based on nanomicelle technology with a concentration of 0.09%[32]. This nanomicellar formulation could be more effective in delivering the cyclosporine to the tissues[33] and have been shown to reduce ocular surface staining[34, 35], to increase tear volume[36, 37] and to be safe[38]. Adverse events that are known to this product are mild, such as transient pain at instillation for about 23% of patients[38].

Intense pulsed light (IPL) is a therapeutic process that has been used for many years in dermatology and esthetics[39]. The noncoherent pulses of light produce photo-biochemical effects and, in the treatment of dry eye disease, the application on the skin around the orbit to produces these effects on the meibomian glands and their surrounding tissue[40]. The mechanisms by which IPL improves signs and symptoms of dry eye are not fully understood, but the melting of the meibum, the clogging of telangiectatic inflammatory vessels, the reduction of epithelial turnover, the improvement in the collagen synthesis, a mitochondrial activity enhancement (photo modulation), and the destruction of parasitic and bacterial species are the main theoretical explanations[41-43]. IPL has been shown to be an effective therapeutic option to manage MGD[44-47]. Dozens of studies have shown that IPL reduces dry eye symptoms, increases tear break-up time, improves the secreting function of the glands as well as the quality of the meibum and reduces corneal staining[43, 48]. The optimal number of IPL sessions for an effective dry eye treatment have not been established, but many studies use 3 sessions, which is the starting point of many clinicians[49]. IPL is often combined with meibomian gland expression to maximize the therapeutic effects[50]; however, controlled studies have shown that IPL is largely responsible of these effects and that it is the core mechanism of this combination[51-53]. Two studies have observed the effect of IPL on contact lens users, with the conclusion that it is an effective treatment for this population[54, 55]. IPL is considered to be a safe treatment[56], but localized redness and burning sensation or tenderness can occur following the treatment[43]. Loss of eyelashes have been reported[52]. More severe events, although rare, can include skin depigmentation and keloids[43].

Objectives

The primary objective of this study is to determine whether the combination of 0.09% cyclosporin ocular nanomicellar drop treatment for 16 weeks and three IPL sessions is more efficient than the combination of 0.09% cyclosporin ocular nanomicellar drop with three sham IPL sessions in relieving the symptoms of symptomatic soft contact lens wearers. The secondary objective is to do the same comparison but when studying signs of dry eye (TBUT, NIBUT, tear osmolarity, tear meniscus height, meibomian gland

atrophy, corneal staining and conjunctival staining) in soft contact lens wearers. The third objective of this study is to explore the effect of Cequa alone on symptoms and signs of contact lens wearers that suffer from dry eye. The fourth objective is to assess the security profile of the treatments on soft contact lens wearers.

Hypothesis

It is believed that the experimental group (receiving Cequa and IPL) will have a greater improvement in symptoms of dry eye while wearing contact lenses when compared to the control group. Previous studies have shown that cyclosporine A can improve dry eye symptoms[27, 57, 58]. Even though results using the previous formulation on contact lens wearers have been modest[28-30], the proven role of inflammation in contact lens dry eye[21, 59-61] theoretically supports that its new formulation could help the signs and symptoms of contact lens dry eye. It will be combined to a MGD treatment, which has been shown in the past to enhance effects on contact lens wearers[30]. IPL has been shown in multiple studies to improve dry eye signs and symptoms[43-48].

Specifically, tear film stability is expected to be improved in the experimental group when compared to the control group, given the proven effect of IPL on meibomian function and tear film stability[44-46, 51, 52, 62-65]. No significant differences in corneal staining and conjunctival staining scores between the two groups are expected, as the results of studies testing IPL on non-CL wearers are very sparse on these variables, and contact lens wearers frequently have mechanical or mild toxic causes (maintenance solution) that maintain these corneal or conjunctival epithelial defects. No significant difference in tear osmolarity is expected between the two groups either, as the results of studies testing IPL on non-CL wearers are very sparse on this variable. No significant difference in gland atrophy score in either group is also expected, as the results of studies testing the IPL on LC non-carriers are very sparse regarding this variable. Also, the researchers' view is that a gland that is atrophied may recover the part that was recently in the process of atrophy, resulting in a slight improvement on meibography, but the morphological changes caused by atrophy are essentially permanent. It is expected also that no serious adverse effect will happen in none of the two groups, as both treatments have been shown in previous studies to have good security profiles[36, 56]. No significant difference is thus expected between the two groups regarding adverse effects.

Trial design

This study is a pre-post interventional study randomized on the IPL intervention; it is a superiority randomized clinical trial sham-controlled. It will be composed of two groups of equal sizes (1:1 allocation ratio).

METHODS

Study setting

This study will take place in an optometric private practice clinic in Sherbrooke, Canada. Data will be stored and analyzed in a university research center in the same city.

Eligibility criteria

The inclusion criteria for this study are the following:

- 18 years or older and able to consent
- Silicone-hydrogel contact lens wearers (minimum wear of 1 day/week for 4 hours) since at least 2 years
- Patients that use monthly, bi-monthly or daily replaceable soft contact lenses
- Symptomatic contact lens wearers (f-CLDEQ-8 score of 12 or above)

The exclusion criteria for this study are the following:

- Present or past usage of Cequa
- Usage of cyclosporin drop in the past 6 months
- Known cyclosporin intolerance
- Current pregnancy or breastfeeding
- IPL or cyclosporin contraindication (ocular HSV infection history, active ocular infection, usage of medication that induces sensitivity to light, epilepsy, history of skin cancer in the treatment area, pigmented lesion in the treatment area, keloid scar in the treatment area, tattoo in the treatment area, vitiligo)
- Refractive surgery in the past 12 months
- Thermal pulsation MGD treatment in the past 12 months
- Usage of topical glaucoma treatment
- Continuous wear of contact lenses (sleeping with contact lenses)
- Poor fit of contact lenses (decentered or excessive movement)
- Giant papillary conjunctivitis

Who will take informed consent?

All procedures will be performed by the same licensed optometrist. This researcher or another member of the research team (if participant is, for instance, a patient of the optometrist) will collect informed consent.

INTERVENTION

Explanation for the choice of comparators

It was decided that a sham IPL procedure would take place. To perform such a sham, a piece of hardened plastic has been designed with a 3D printer that covers the prism of the IPL, blocking the light's energy from reaching the skin of the participant. A 5mm space between the surface of the prism and the piece of plastic with openings on the side will allow the light to be ejected to the side. This will both prevent reflection of the energy, which could have damaged the IPL and will allow for the participant to see some light through his eyeshields. This will assure that the visual and auditive experience of participants in the sham group is very close to that of a real IPL experience. Of course,

participants will have protective shields on their closed eyelids, which will make them unable to see the piece of plastic. Figure 1 shows a picture of the blocker.

Figure 1: Picture of the IPL filter over the M22 Lumenis prism

Intervention description

Participants will receive drops of 0.09% cyclosporine twice a day for 16 weeks in both eyes. The product is distributed in single-dose vials, which will require the use of a different vial for the morning and the evening dose. Instructions will be given to the participants that they leave a time gap of 15 minutes between the instillation of the cyclosporine drops and the insertion of their contact lenses. In the same way, it will be instructed that participants wait 15 minutes after removal of the contact lenses before instillation if the drops.

The second intervention will be a standard IPL procedure for the experimental group, as described by Toyos[62]. First, protective opaque shields will be placed on the closed eyelids of the participants, closely under the inferior lid margin. Then, protective IPL gel will be applied in the treatment zone, that will go from the right temple to the left temple, boarding the inferior limit of the shield and including the zone over the nasal bone. Setting of cooling of the IPL prism will be activated and the 590nm filter will be placed in the handheld part of the IPL. 3 pulsations per shot and cycles of 6-50 ms (pulse-pause) for each pulsation will be programed. Fluence of the IPL will be adjusted depending on the skin type (using the Fitzpatrick scale; type I receiving a fluence of 16 J/cm^2 and type IV receiving a fluence of 13 J/cm^2). 15 shots of IPL will be applied from one temple to the other, slightly overlapping each precedent shot (7 shots on each side and one central shot; see figure 2). This procedure will be repeated for a second passage, for a total of 30 IPL shots on the treatment zone.

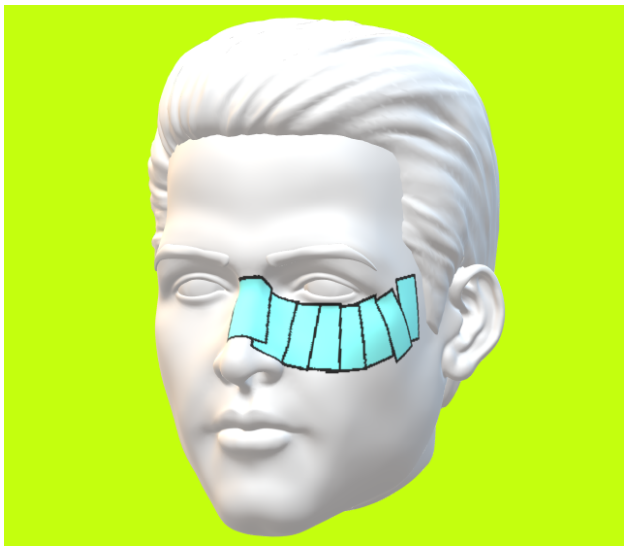

Figure 2: Half of one passage of IPL treatment plan

Criteria for discontinuing or modifying allocated interventions

Either one of the interventions would be discontinued for a participant if a serious adverse event arose. Serious adverse events will be described in this study as event possibly linked to the intervention that require medical management (prescription of antimicrobial or anti-inflammatory drugs, surgery) and/or that poses the threat of long-term visual sequelae. It is expected that participants feel a slight level of discomfort with both interventions (cyclosporine drops and IPL session), so this will not be a factor. Participants' will to stop the study would also be a motive of discontinuation of the assigned treatment. In no case would a participant be transferred to the other group of the study.

Strategies to improve adherence to interventions

Non-adherence could be a problem for the first intervention (cyclosporine eyedrops). To try and improve adherence, a courtesy call will be made by the research team 3 weeks after the beginning of the study. Participants will also receive a question by text message weekly to ask about the number of drops instilled in the last days, which could be a reminder to observe the treatment. Concerning the IPL, it is not expected that adherence will be a problem since this intervention is made in the clinic and only takes a few minutes. However, financial compensation will be given to the participants for their time, which should help even more to ensure adherence to this treatment.

Relevant concomitant care permitted or prohibited during the trial

Participants will be permitted to continue any dry eye treatments that they are currently taking (besides those mentioned in the exclusion criteria). This includes use of artificial tears, lubricating ointments, omega-3 supplements, warm compresses, lid hygiene, punctal plugs, etc.). However, the initiation of new components of treatment will not be permitted during the 4 months of the trial.

Provisions for post-trial care

Participants from the study will be patients of the practice in which the optometrist that is the main investigator of this study works. Dry eye care will continue with this optometrist if the patient wishes to pursue care with this optometrist or any other of the clinic.

Outcomes

The primary outcome of this study will be participants' symptoms of dry eye while wearing contact lenses. It will be collected at each visit using the f-CLDEQ-8 at every visit of every participant. This French version of the CLDEQ-8 has shown to be valid, with an internal consistency of $\alpha = 0.929$ and a high reliability (ICC=0.944)[66]. The use of the CLDEQ-8 is recommended by the Tear Film Ocular Surface Society (TFOS) panel[67] to measure this outcome. For each participant in a given group, the difference between the score at the beginning of the study (baseline) and at the end of the study (16 weeks) will be calculated. The mean difference of each group will be calculated and compared between groups. The CLDEQ-8 is a responsiveness tool that has been deemed efficient to measure change in contact lens comfort in studies with a clinically important difference (CID) value of 3 points on 37[68]. Alternatively, questions will be sent by electronic communication to the participants twice weekly to ask about their perceived comfort while wearing contact lenses (scale 0-100). The use of such a global rating scale of change is recommended by the TFOS panel[67] and will allow for a different, more continuous and global evaluation of symptoms. In these electronic communications, participants will also be asked the amount of average wearing time of their contact lenses in the past 3 to 4 days and their average daily use of artificial tears in the past 3-4 days, which can be considered indirect markers of contact lens discomfort[67].

There are many secondary outcomes in this study:

- Tear film stability over contact lenses. This outcome will be measured with the Medmont E300 automated Tear Film Surface Quality (TFSQ) and NIBUT functions while the participant is wearing his contact lenses. The average of 3 measures will be selected. It will be collected for each eye.
- Tear film osmolarity while wearing contact lenses. This outcome will be measured using the i-Pen, a portable osmometer which has been shown to be reliable[69], valid and correlated with other signs and symptoms of dry eye[70]. The osmolarity will be collected at the inferior lid for both eyes.
- Tear volume while wearing the contact lenses. This outcome will be measured using the tear meniscus height evaluation of the Myah (Topcon) while the contact lenses are in place in each eye. This function averages 5 points across the tear meniscus to provide a value. The value of tear meniscus height while wearing contact lenses has been shown linked to comfort[71]
- Tear film stability. This outcome is used in a majority of studies on dry eye and will be collected by two manners. First, the automated TFSQ and NIBUT functions of the Medmont E300 corneal topographer will be performed on the tear film (after removal of the contact lenses). It will also be collected by measuring the time between opening of the eyes and a break in the fluoresceine pattern of the

tear film. 30 seconds after a small amount of sodium fluoresceine is instilled from a strip, video recordings from a slit lamp of the surface of the eye with cobalt filter from the slit lamp and a handheld yellow filter will be taken. The average of three measurements will be used.

- Corneal and conjunctival staining score. This outcome will be evaluated by instilling a dye in the eye. Fluoresceine will be used for corneal staining and lissamine green will be used for conjunctival staining. Pictures of the cornea (with cobalt filter and handheld yellow filter) and the conjunctiva will be taken at the slit lamp and sent to the AOS software that objectively grades anterior segment imagery[72]. The conjunctival pictures will be sent to observers blinded to the allocation of the participant for grading. The Efron grading scale will be used, which is specific for contact lens complications, widely used in clinic and one of the most reliable scales available[73]. Ocular surface staining scores have been recommended by the TFOS panel for studies on contact lens dry eye[67].
- Meibomian gland atrophy. This outcome will be evaluated by imaging the inferior and superior eyelids of each eye with the Lipiscan (Johnson & Johnson) of each participant and having a blinded observer grade the meibomian score. The score will be established using Pult's meiboscale, a reliable[74] and repeatable[75] scale.
- Presence of adverse effects. This outcome will be measured using a homemade questionnaire that asks about adverse effects on both interventions (Cequa and IPL). The questionnaire contains yes/no questions as well as open questions, allowing participants to report unexpected or unusual adverse effects.
- Best corrected distance visual acuity. This outcome is measured for security purposes only. It will be measured at each visit before any other action is posed. Best corrected visual acuity is an indicator of good health of the ocular structures.
- Intraocular pressure. This outcome is measured for security purposes only. No documented case of IOP rise following the intake of cyclosporin drops or IPL treatment is known, but in the presence of fairly new therapeutic options (Cequa and IPL), it was decided to measure the pressure.

Participant timeline {13}

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		**Close-out**
TIMEPOINT(Week)	**0**	**8**	**11**	**14**	16
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				

Allocation		X			
INTERVENTIONS:					
0.09% Cyclosporine (Cequa)	←	—	—	—	→
IPL or Sham-IPL		X	X	X	
ASSESSMENTS:					
f-CLDEQ-8	X	X	X	X	X
Use of artificial tears	←	—	—	—	→
Contact lens wear hours	←	—	—	—	→
0-100 comfort	←	—	—	—	→
f-TBUT	X	X			X
NIBUT over SCL	X	X			X
NIBUT on tears	X	X			X
Tear osmolarity	X	X			X
Tear volume (TMH)	X	X			X
Corneal staining	X	X			X
Conjunctival staining	X	X			X
Meibography	X				X
Adverse events questionnaire	X	X	X	X	X
Best-corrected Visual acuity	X	X	X	X	X
Intra-ocular pressure	X	X	X	X	X

Sample size

The number of participants needed to detect a significant between the groups using the f-CLDEQ-8 was established by using data from prior studies[54, 66, 76]. The standard deviation of the sample on the f-CLDEQ-8 was estimated by calculating the standard

deviation of the portion of the sample from the validation study of the f-CLDEQ-8 that had a score≥12. This approach was used because the population from which the sample in both studies (the validation study and the study described in this article) will be drawn are very similar. The expected standard deviation is 4.58. It was decided to use effect size to compute sample size. It was decided that an expected effect size of 0.80 would be used. This comes from subtracting the effect size for symptoms (pre-treatment vs post-treatment) in the study on Cequa by Tauber et al., which was 1.2, from the effect size (IPL vs sham) in the study of Yang et al., which was 2.0. The rationale for this calculation was that both groups will already have had the effect from Cequa when receiving their IPL (or sham-IPL) treatment. 0.80 is also the theoretical value for a large effect size by Cohen. To detect a 0.8 effect size between the two groups with a bilateral T-test for independent samples having a standard deviation of 4.58, a total of 44 participants (22/group) will have to be recruited.

Recruitment

Recruitment for this project will be made directly by the optometrists that practice in the associate locations that surround the clinical center where the research will take place (total of 18 optometrists). When they will see a patient during an eye exam that seems to fit the eligibility criteria, information about the study will be given to the patient and, if desired contact information to the research team. Posters describing the study and including a QR code linked to the email address of the main researcher will also be put up in the optometry clinics of the associate locations (6 clinics) for potential candidates to contact the research team.

Assignment of interventions: allocation

Sequence generation

Allocation of the participants to the two groups will be stratified following the severity of the f-CLDEQ-8 score to avoid too much variability in this important factor in the amplitude of the effect of the treatments[77]. The f-CLDEQ-8 will be established at the first visit and participants will be categorized as having moderate symptoms (score 12 to 17), severe symptoms (score 17 to 24) of very severe symptoms (score 25 or over). Allocation will be performed after the first visit. For each possible category, a random sequence of allocation will be drawn for the 6 first participants that are associated to that category. Allocation will follow the sequence in the order in which participants contacted the research team to participate in the study. A list of all possible allocation sequences associated with a number has been established and a computerized random number generator will be used to generate the number representing a sequence for each of the categories. After the 6 first participants from a category are randomized, another number will be generated to identify the sequence used for the next series of 6 participants of that category. This will also allow for an equal number of participants to be allocated in each group.

Concealment mechanism

This does not apply to this study, for the conduct of the study from the participant's point of view will be the same in both groups and that the main researcher will not be blinded to the allocation.

Implementation

The main researcher or his research assistant will be the one performing the enrolment of the participants. However, the allocation to the groups will be determined by another researcher, that is not implicated in the recruitment. This second researcher will be the only person to have access to the allocation sequences and will assign participants to the groups chronologically by the date at which contact was established between the participant and the research time, as reported by the researchers implicated in the recruitment and enrolment.

Assignment of interventions: Blinding

Who will be blinded

Participants will be blinded to their own allocation to one of the two groups. Since opaque eye shields are a safety requirement to perform an IPL treatment, participants will not see the researcher apply (or not apply) the light blocker on the IPL to perform a sham procedure. Members of the research team that will analyse the data (grading of the conjunctival scores) will also be blinded to the allocation of the participant from which the data has been collected. This will be easy to ensure as the videos and images will be sent digitally to these members of the research team. The researcher that will physically perform the collect of data and the interventions (IPL or sham-IPL) will not be blinded, for this was not possible given the available resources and the safety of the IPL procedure.

Procedure for unblinding if needed

The only reason for which a participant would be unblinded in this study is if a participant reported persistent visual disturbance following an intervention session (IPL or sham-IPL) and that BCVA was found to be decreased compared to the usual BCVA of the patient. The allocation would be revealed to the participant and participation to the study would end.

Data collection and management

Plans for assessment and collection of outcomes

Main data collection will be done at visit 1 for baseline, visit 2 and visit 5 for all outcomes (see participant timeline, number 13) except for meibography, that will only be done at visit 1 and visit 5. Primary outcome (f-CLDEQ-8 questionnaire) will be assessed at every visit. The f-CLDEQ-8 has been shown to have good reliability (ICC=0.944) and internal consistency (Cronbach α=0.928) and to be well correlated with overall opinion of the contact lens[66]. The original CLDEQ-8 has a diagnostic criteria of 12 points or more and a MCID of 3 points as well as a good responsiveness[68] and very good dose-response[78] relationship to overall opinion of contact lens. Its use is recommended by the TFOS group in the International Workshop on Contact Lens Discomfort[67] as it is the only short and validated tool to be specific to contact lens dry eyes. This group also suggests that questioning participants in clinical trial on their daily wearing time could be an effective way of evaluating treatment effects and that numerical global scales can be used to evaluate contact lens comfort[67].

TBUT using fluoresceine is the standard tear stability measurement, that has been shown to have a sensitivity of 72.2% and a specificity of 61.6% when a diagnostic value of 10 seconds is used[79]. It will be established from the slit lamp through a cobalt filter and a handheld yellow filter to enhance visibility of the fluoresceine. 3 readings will be taken for each eye. The measuring of NIBUT with the TFSQ function of the Medmont topographer have shown to be repeatable and to have a sensitivity of 82% and a specificity of 94% for diagnosing dry eye with a cut-off of 12.1 seconds[80]. The validity of NIBUT and TFSQ over contact lens using the Medmont function has not been studied in published work; however it has been used in a RCT in 2018[60].

Tear osmolarity will be measured using the i-Pen handheld osmometer. This instrument has been shown to be well correlated with other signs and symptoms of dry eye and to have a sensitivity of 90.9% and a specificity of 90.6% to diagnose dry eye disease when a value of 318 mOsm/L is used as a criteria[69]. In vitro studies have also reported good repeatability and validity in determining the osmolarity of solutions[70]. The osmolarity of the inferior palpebral conjunctiva will be measured in this study with the participants' contact lenses still in place. This will prevent the influence of reflex tearing from contact lens removal on osmolarity[81].

Tear volume while the contact lenses are in place will be evaluated by measuring the tear meniscus height using the MyAh automated function, which measures the height automatically in 5 different points of the inferior meniscus. No validated study has been published on the measurement of this variable by the MyAh.

To assess corneal and conjunctival staining, sodium fluoresceine and lissamine green will be instilled in the inferior fornix of the conjunctiva of each eye and picture will be taken through the slit lamp (with cobalt and handheld yellow filter for cornea and with no filter for conjunctiva) for blinded grading. The AOS system has been shown to have good reliability in grading anterior segment signs[72] and will be used to grade corneal staining by running the pictures through the AOS platform. The Efron grading scale will be used for conjunctival staining; it has been shown to have an inter-rater repeatability of 0.67 and is a tool specific for contact lens users[73].

The degree of atrophy of the meibomian glands will be assessed by imaging the glands of both lids of each eye with the Lipiscan meibograph. Images will be sent for blinded

grading using Pult's meiboscale to determine the meiboscore (level of atrophy graded from 0 to 4). It is the subjective grading scale that has been shown to have the best repeatability[75], as well as high inter-rater and intra-rater reliabilities[74].
Intra-ocular pressure will be measured using a non-contact tonometer (air puff) to avoid instilling anaesthetic drops in the participants' eyes.

Plans to promote participant retention and complete follow-up

Two strategies will be used in order to enhance participants' retention in the study. First, a courtesy call will be made to participants 3 weeks after visit#1 to see if they are using the drops as required in the study, if they have concerns about the study and to encourage continuing participation in the clinical trial. Second, financial compensation will be given to the participants for the time that they commit to the study. Visits 1,2 and 5 (which include complete data collection) will be compensated with 40$ while visits 3 and 4 will be compensated with 20$.

Data management

A paper sheet will be used to record data that is not an image or a video (BCVA and IOP) and to take notes on the capture of images and videos during the collection of data visits by participants. In every instrument, the notation will be similar and will not include the name or allocation of participants (participantID_V1_NIBUT_OD for instance). The sheet will also be used to document the treatments given. Data will be stored on password protected computers in the clinic (connected to secure cloud backups) and the sheets of paper will be kept locked at the research centre on aging of University of Sherbrooke in the office of the main researcher.

Confidentiality

Alpha-numerical participant IDs will be assigned to the participants and will be used to name participants in every document related to the study except for the consent form, which will be kept in a secure and locked drawer in the office of the main researcher at the research centre on aging of the University of Sherbrooke. A password-secure document will also exist on a single computer linking the participants ID to participants' names and will be available only to the main researcher and his research assistant.

Statistical methods

Statistical methods for primary and secondary outcomes

Primary outcome will be the change from baseline to week 16 on the average score of the f-CLDEQ-8 of each group. A two-tailed t-test for independent samples will be conducted to evaluate statistical significance of the difference of the change between the two groups. T-tests for the difference between the average score of all participants

on the f-CLDEQ-8 at baseline and the average score of all participants at week 8 will also be conducted to evaluate the effect of Cequa alone on contact lens users.
Other measurements of participants' symptoms will generate a large number of data and a longitudinal analysis regression model will be used, as it is appropriate for repeated measures on subjects.
Concerning the secondary outcomes, the statistical methods used will depend on the nature of the variable and in a way that takes in account the inter-eye correlation of a given participant. Continuous variables (f-TBUT, NIBUT, tear osmolarity, tear meniscus height, that will be collected on both eyes of each participant, will be analysed using a multi-level model. Categorical variables (Meibomian gland atrophy score, corneal staining score and conjunctival staining score) will be analysed using a general linear model (GLM).

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

In case of dropouts of the study, consent to continue limited contact will be asked to dropout participants. The f-CLDEQ-8 will still be sent to dropout participants for completion at the originally scheduled data collection times to avoid missing data. Analysis will be made in intent-to-treat principle. Non-adherence will not be mitigated by statistical methods to avoid introducing bias in the conclusions of the study.

Plans to give access to the full protocol, participant level-data and statistical code

Access to the full protocol and data will be available upon individual requests any time after publication of the results of this clinical trial. However, in order to gain access to this information, requesters will have to be verified scholars, clearly state the motive for which the data is wanted and a plan to securely store the data.

Oversight and monitoring

Composition of the data monitoring committee

A data monitoring/coordinating committee has been formed and is composed of the optometrist that is the owner of the clinic in which the study takes place, one independent clinician optometrist with a research training, one professor at another university (School of Optometry of University of Montreal) and one statistical expert from the establishment in which the study is done (University of Sherbrooke, Centre of Research on Aging). The committee will meet after 1/3 of the participants have finished their implication in the study, after 2/3 of the participants have finished their implication in the study and after data collection is over for all participants.

Adverse event reporting and harms

Adverse events will be inventoried with a homemade questionnaire. Participants are first asked to describe on a Likert scale the intensity of their discomfort and of their blurry vision while instilling the Cequa drops. There is then an open question about other side effects that they think are linked to the Cequa eyedrop.
The second part of the questionnaire asks about adverse effects of IPL. Participants are to report the presence/absence and grade (0-10 if present) the following side effects: peri-ocular pain, eye pain, sensation of burning, eyelash loss, redness of the eyes, redness of the skin and blurry vision. Separate questions concern the time during the procedure, in the following 12 hours and in the following 3 weeks. An open question also allows participants to describe and grade other side effects that they attribute to the IPL.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

The ethics committee will be notified by the web platform as soon as an amendment is made to the protocol and the research will pause until authorization is given from the committee. Members of the research team that are not implicated directly in data collection will be notified by email.
Participants will be contacted by telephone, including those who have already completed the study. Consent of the amended protocol will be obtained once again from each participant with emphasis on the changes made from the original.

Dissemination plans

Poster presentations and peer-reviewed publications (between 1 and 4) will serve to communicate the results of this study with the scientific community. Each publication will be on a specific aspect of the data and, possibly, on secondary analysis of the data.

Discussion

Some aspects of this project have, to the author's knowledge, never been studied before. For instance, no data currently exist on the effect of Cequa eyedrop on contact lens users. The combination of cyclosporine and IPL treatments have also never been studied. In the absence of a suitable comparator and given the exploratory nature of the objective 3, it has been decided that this before-after comparison (with no placebo against Cequa) would be of interest, even though the risk of bias is stronger with such a study design.

It has also decided that recruitment would be large in order to represent a large portion of uncomfortable contact lens wearers that clinicians see in their practices on a daily basis. Dry eye disease and contact lens discomfort being conditions that are, in essence,

symptomatic, it has been decided that recruitment would focus on symptoms rather than having eligibility criteria based on clinical signs or diagnostic.

The biggest practical issue in this study is that it was not possible to make it double-blind. The main researcher will also be the one collecting the data and performing the treatments. Given the nature of the IPL treatment, it was not possible to conceal from the researcher performing it the allocation of the participants. However, almost all the data will be analysed by raters (or automatic systems) that are not aware of the allocation of the participants.

Another issue is that a few effects could require careful considered before drawing conclusions from this clinical trial. The order effect, in which the order of administration of treatments influence how they are effective, is possible. For instance, it would be possible that the Cequa treatment targets some of the action sites of the IPL treatment and already has a therapeutic effect, lessening the efficacy of the IPL. Also, the dose-response effect could play a role in this study. This effect, also seen in clinical practice, concerns situations in which the repeated administration of a treatment (resulting in an increase in dosage over time) amplifies its therapeutic effect. In the present study, the Cequa drop will be used twice a day for the whole 4 months. Studies on Cequa has shown that some signs reach their peak improvement after 56 days (about 2 months)[76], while others seem to continue improving beyond day 56[34]. The improvements due to the cumulated dose of Cequa could be undistinguishable from the effect of IPL (and its cumulated dose after 3 treatments) in the final data collection.

Compliance is another issue that could arise in this study. The Cequa treatment being applied at home by participants, it is difficult to monitor thoroughly their compliance to it. On the other hand, the IPL treatment is applied by the research team in the clinic. Thus, compliance issues only apply to one of the treatments of the study. It will be monitored twice a week by an electronically sent question asking how many doses were forgotten in the past days. Although imperfect, this method lessens the burden for participants when compared to other methods frequently used, like the gathering of used vials, which have also been shown to be subject to important bias[82].

The choice of variables to collect was also an issue while designing this study, given the lack of consensus on the best clinical outcomes to characterize contact lens dry eye and discomfort[67] and what was possible to do in the context of this study. Choices were made to favour objective outcomes that have been studies in the past and that are relevant to the treatments. Rapidity and comfort for the participants was also taken into account.

There are many strengths in this study. The randomization of participants should minimize bias that would arise from a difference in characteristics between the two groups. The presence of the control group will allow the research team to study the effects of adding IPL to a contact lens wearers already taking cyclosporine drops. It will

allow to isolate the effect of IPL and to make sure that the possible improvement does not come from other elements (such as the psychological effects of receiving treatment). The continued improvement in the condition that the cyclosporine drop could provide will be monitored due to the control group. Also, in this study, the clinicians that will grade the conjunctival staining score and the meibography score will be blinded to the allocation of the participants. Corneal staining will be graded by an objective artificial intelligence platform, adding even more objectivity and consistency to the results. The main outcome also is collected using the f-CLDEQ-8, a validated translation of the CLDEQ-8, which is the main questionnaire seen in studies to assess contact lens discomfort. Finally, the use of statistical methods that consider the correlation between the two eyes of a given participant allows for full usage of the collected data without increasing the risk of type I errors; it is a recommended approach in dealing with the inter-eye statistical challenge[83].

One of the limits of this study is the great number of confounding factors that exist in contact lens discomfort. It can be caused and influenced by many different elements (material of the lens, contact lens wear history, curvature, solution used, modulus of the lens, toricity, environment, occupation, make-up, etc.) which could not be all accounted for and could influence the efficacy of the treatments. The study also lacks a direct measurement of inflammation. MMP-9 is the marker that can be measured with commercial equipment; however, the cost of this machine could not be fitted in the budget of the study. Osmolarity, however, will be measured, which has been shown to correlate well with MMP-9 levels[84]. Another limit is that the researcher that will be performing the treatments will not be blinded to the allocation. In the context of a treatment that has to be performed in clinic and requires some skills, it was not possible for this member of the research team to be blinded to the allocation. Finally, a limit resides in the fact that the main outcome is based on subjective impressions of the participants. Bias of social desirability or enthusiasm of the participants could impact the measured change in symptoms.

Trial status

A pilot study was conducted in the fall of 2023 and recruitment for the official RCT should start in April 2024. Version #3 of the protocol (February 2024) is the protocol that is currently being used. Recruitment is expected to finish in October or November of 2025.

Abbreviations

MGD: Meibomian Gland Dysfunction
IPL: Intense Pulsed Light
TBUT: Tear Break-Up Time
NIBUT: Non-Invasive Break-Up Time

f-TBUT: Tear Break-Up Time measured using sodium fluoresceine
f-CLDEQ-8: French version of the Contact Lens Dry Eye Questionnaire-8
TMH: Tear Meniscus Height
SCL: Soft Contact Lens
BCVA: Best Corrected Visual Acuity
IOP: Intra-Ocular Pressure
MCID: Minimal Clinically Important Difference
TFOS: Tear Film Ocular Society
GLM: General Linear Model
RCT: Randomized Clinical Trial
TFSQ: Tear Film Surface Quality

Declarations

Funding

This study has three sources of funding. First, part of it will be auto-funded by the researchers' personal funds. Secondly, the Canadian Optometric Trust Fund (COETF) gave a 1500$ award in 2021 to help fund the project. Thirdly, and most importantly, the project is funded through a MITACS grant (15,000$). This was made possible by the contribution of half of this amount by Sun Pharma. The company also provides the Cequa drops used during the study free of charge.

Ethics approval and consent to participate

This project has been approved by the *Comité d'éthique à la recherche du CIUSSS de l'Estrie-CHUS* (project number 2024-5200). All material related to the project, including consent forms, questionnaires, recruitment documents, funding, and scientific relevance have been reviewed and approved by this committee.

Participants will be given an information and consent form that is written in simple language. This document, available in English and in French, will be given to the participants by email before planning visit#1 to give them time to review the information. The research team will be available by email or telephone if the participants have any questions. Consent to participate will be renewed before each treatment and participants will be free to withdraw at any moment without justification.

References

1. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017;15(3):276-83.
2. Papas EB. The global prevalence of dry eye disease: A Bayesian view. Ophthalmic Physiol Opt. 2021;41(6):1254-66.

3. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II Epidemiology Report. Ocul Surf. 2017;15(3):334-65.
4. Rouen PA, White ML. Dry Eye Disease: Prevalence, Assessment, and Management. Home Healthc Now. 2018;36(2):74-83.
5. Chhadva P, Goldhardt R, Galor A. Meibomian Gland Disease: The Role of Gland Dysfunction in Dry Eye Disease. Ophthalmology. 2017;124(11S):S20-S6.
6. Hassanzadeh S, Varmaghani M, Zarei-Ghanavati S, Heravian Shandiz J, Azimi Khorasani A. Global Prevalence of Meibomian Gland Dysfunction: A Systematic Review and Meta-Analysis. Ocul Immunol Inflamm. 2021;29(1):66-75.
7. Schaumberg DA, Nichols JJ, Papas EB, Tong L, Uchino M, Nichols KK. The international workshop on meibomian gland dysfunction: report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. Invest Ophthalmol Vis Sci. 2011;52(4):1994-2005.
8. Gomes JAP, Azar DT, Baudouin C, Efron N, Hirayama M, Horwath-Winter J, et al. TFOS DEWS II iatrogenic report. Ocul Surf. 2017;15(3):511-38.
9. Dumbleton K, Caffery B, Dogru M, Hickson-Curran S, Kern J, Kojima T, et al. The TFOS International Workshop on Contact Lens Discomfort: report of the subcommittee on epidemiology. Invest Ophthalmol Vis Sci. 2013;54(11):TFOS20-36.
10. Koh S. Contact Lens Wear and Dry Eye: Beyond the Known. Asia Pac J Ophthalmol (Phila). 2020;9(6):498-504.
11. Chalmers RL, Young G, Kern J, Napier L, Hunt C. Soft Contact Lens-Related Symptoms in North America and the United Kingdom. Optom Vis Sci. 2016;93(8):836-47.
12. Sulley A, Young G, Hunt C, McCready S, Targett MT, Craven R. Retention Rates in New Contact Lens Wearers. Eye Contact Lens. 2018;44 Suppl 1:S273-S82.
13. Willcox MDP, Argueso P, Georgiev GA, Holopainen JM, Laurie GW, Millar TJ, et al. TFOS DEWS II Tear Film Report. Ocul Surf. 2017;15(3):366-403.
14. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15(3):438-510.
15. Guillon M, Maissa C. Contact lens wear affects tear film evaporation. Eye Contact Lens. 2008;34(6):326-30.
16. Nichols JJ, Sinnott LT. Tear film, contact lens, and patient-related factors associated with contact lens-related dry eye. Invest Ophthalmol Vis Sci. 2006;47(4):1319-28.
17. Alghamdi WM, Markoulli M, Holden BA, Papas EB. Impact of duration of contact lens wear on the structure and function of the meibomian glands. Ophthalmic Physiol Opt. 2016;36(2):120-31.
18. Ucakhan O, Arslanturk-Eren M. The Role of Soft Contact Lens Wear on Meibomian Gland Morphology and Function. Eye Contact Lens. 2019;45(5):292-300.
19. Insua Pereira E, Sampaio AP, Lira M. Effects of contact lens wear on tear inflammatory biomarkers. Cont Lens Anterior Eye. 2022;45(5):101600.
20. Alzahrani Y, Colorado LH, Pritchard N, Efron N. Longitudinal changes in Langerhans cell density of the cornea and conjunctiva in contact lens-induced dry eye. Clin Exp Optom. 2017;100(1):33-40.

21. Efron N. Contact lens wear is intrinsically inflammatory. Clin Exp Optom. 2017;100(1):3-19.
22. Periman LM, Mah FS, Karpecki PM. A Review of the Mechanism of Action of Cyclosporine A: The Role of Cyclosporine A in Dry Eye Disease and Recent Formulation Developments. Clin Ophthalmol. 2020;14:4187-200.
23. Wan KH, Chen LJ, Young AL. Efficacy and Safety of Topical 0.05% Cyclosporine Eye Drops in the Treatment of Dry Eye Syndrome: A Systematic Review and Meta-analysis. Ocul Surf. 2015;13(3):213-25.
24. Rao SN. Topical cyclosporine 0.05% for the prevention of dry eye disease progression. J Ocul Pharmacol Ther. 2010;26(2):157-64.
25. Chen M, Gong L, Sun X, Xie H, Zhang Y, Zou L, et al. A comparison of cyclosporine 0.05% ophthalmic emulsion versus vehicle in Chinese patients with moderate to severe dry eye disease: an eight-week, multicenter, randomized, double-blind, parallel-group trial. J Ocul Pharmacol Ther. 2010;26(4):361-6.
26. Prabhasawat P, Tesavibul N, Mahawong W. A randomized double-masked study of 0.05% cyclosporine ophthalmic emulsion in the treatment of meibomian gland dysfunction. Cornea. 2012;31(12):1386-93.
27. Chen D, Zhang S, Bian A, Hong J, Deng Y, Zhang M, et al. Efficacy and safety of 0.05% cyclosporine ophthalmic emulsion in treatment of Chinese patients with moderate to severe dry eye disease: A 12-week, multicenter, randomized, double-masked, placebo-controlled phase III clinical study. Medicine (Baltimore). 2019;98(31):e16710.
28. Hom MM. Use of cyclosporine 0.05% ophthalmic emulsion for contact lens-intolerant patients. Eye Contact Lens. 2006;32(2):109-11.
29. Willen CM, McGwin G, Liu B, Owsley C, Rosenstiel C. Efficacy of cyclosporine 0.05% ophthalmic emulsion in contact lens wearers with dry eyes. Eye Contact Lens. 2008;34(1):43-5.
30. Wang L, Chen X, Hao J, Yang L. Proper balance of omega-3 and omega-6 fatty acid supplements with topical cyclosporine attenuated contact lens-related dry eye syndrome. Inflammopharmacology. 2016;24(6):389-96.
31. Jerkins GW, Pattar GR, Kannarr SR. A Review of Topical Cyclosporine A Formulations-A Disease-Modifying Agent for Keratoconjunctivitis Sicca. Clin Ophthalmol. 2020;14:481-9.
32. Mandal A, Gote V, Pal D, Ogundele A, Mitra AK. Ocular Pharmacokinetics of a Topical Ophthalmic Nanomicellar Solution of Cyclosporine (Cequa(R)) for Dry Eye Disease. Pharm Res. 2019;36(2):36.
33. Weiss SL, Kramer WG. Ocular Distribution of Cyclosporine Following Topical Administration of OTX-101 in New Zealand White Rabbits. J Ocul Pharmacol Ther. 2019;35(7):395-402.
34. Malhotra R, Devries DK, Luchs J, Kabat A, Schechter BA, Shen Lee B, et al. Effect of OTX-101, a Novel Nanomicellar Formulation of Cyclosporine A, on Corneal Staining in Patients With Keratoconjunctivitis Sicca: A Pooled Analysis of Phase 2b/3 and Phase 3 Studies. Cornea. 2019;38(10):1259-65.

35. Smyth-Medina R, Johnston J, Devries DK, Jasper A, Kannarr SR, Schechter BA, et al. Effect of OTX-101, a Novel Nanomicellar Formulation of Cyclosporine A, on Conjunctival Staining in Patients with Keratoconjunctivitis Sicca: A Pooled Analysis of Phase 2b/3 and 3 Clinical Trials. J Ocul Pharmacol Ther. 2019;35(7):388-94.
36. Sheppard J, Kannarr S, Luchs J, Malhotra R, Justice A, Ogundele A, et al. Efficacy and Safety of OTX-101, a Novel Nanomicellar Formulation of Cyclosporine A, for the Treatment of Keratoconjunctivitis Sicca: Pooled Analysis of a Phase 2b/3 and Phase 3 Study. Eye Contact Lens. 2020;46 Suppl 1:S14-S9.
37. Toyos M, Gupta PK, Mitchell B, Karpecki P. The Effect of OTX-101 on Tear Production in Patients with Severe Tear-deficient Dry Eye Disease: A Pooled Analysis of Phase 2b/3 and Phase 3 Studies. Curr Eye Res. 2022;47(2):220-4.
38. Sheppard J, Bergmann M, Schechter BA, Luchs J, Ogundele A, Karpecki P. Phase 3 Efficacy (Worse-Eye Analysis) and Long-Term Safety Evaluation of OTX-101 in Patients with Keratoconjunctivitis Sicca. Clin Ophthalmol. 2021;15:129-40.
39. Raulin C, Greve B, Grema H. IPL technology: a review. Lasers Surg Med. 2003;32(2):78-87.
40. Rennick S, Adcock L. Intense Pulsed Light Therapy for Meibomian Gland Dysfunction: A Review of Clinical Effectiveness and Guidelines. CADTH Rapid Response Reports. Ottawa (ON)2018.
41. Dell SJ. Intense pulsed light for evaporative dry eye disease. Clin Ophthalmol. 2017;11:1167-73.
42. Giannaccare G, Taroni L, Senni C, Scorcia V. Intense Pulsed Light Therapy In The Treatment Of Meibomian Gland Dysfunction: Current Perspectives. Clin Optom (Auckl). 2019;11:113-26.
43. Suwal A, Hao JL, Zhou DD, Liu XF, Suwal R, Lu CW. Use of Intense Pulsed Light to Mitigate Meibomian Gland Dysfunction for Dry Eye Disease. Int J Med Sci. 2020;17(10):1385-92.
44. Craig JP, Chen YH, Turnbull PR. Prospective trial of intense pulsed light for the treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2015;56(3):1965-70.
45. Piyacomn Y, Kasetsuwan N, Reinprayoon U, Satitpitakul V, Tesapirat L. Efficacy and Safety of Intense Pulsed Light in Patients With Meibomian Gland Dysfunction-A Randomized, Double-Masked, Sham-Controlled Clinical Trial. Cornea. 2020;39(3):325-32.
46. Xue AL, Wang MTM, Ormonde SE, Craig JP. Randomised double-masked placebo-controlled trial of the cumulative treatment efficacy profile of intense pulsed light therapy for meibomian gland dysfunction. Ocul Surf. 2020;18(2):286-97.
47. Toyos R, Desai NR, Toyos M, Dell SJ. Intense pulsed light improves signs and symptoms of dry eye disease due to meibomian gland dysfunction: A randomized controlled study. PLoS One. 2022;17(6):e0270268.
48. Miao S, Yan R, Jia Y, Pan Z. Effect of Intense Pulsed Light Therapy in Dry Eye Disease Caused by Meibomian Gland Dysfunction: A Systematic Review and Meta-Analysis. Eye Contact Lens. 2022;48(10):424-9.
49. Vegunta S, Patel D, Shen JF. Combination Therapy of Intense Pulsed Light Therapy and Meibomian Gland Expression (IPL/MGX) Can Improve Dry Eye Symptoms and

Meibomian Gland Function in Patients With Refractory Dry Eye: A Retrospective Analysis. Cornea. 2016;35(3):318-22.
50. Sambhi RS, Sambhi GDS, Mather R, Malvankar-Mehta MS. Intense pulsed light therapy with meibomian gland expression for dry eye disease. Can J Ophthalmol. 2020;55(3):189-98.
51. Arita R, Fukuoka S, Morishige N. Therapeutic efficacy of intense pulsed light in patients with refractory meibomian gland dysfunction. Ocul Surf. 2019;17(1):104-10.
52. Rong B, Tang Y, Tu P, Liu R, Qiao J, Song W, et al. Intense Pulsed Light Applied Directly on Eyelids Combined with Meibomian Gland Expression to Treat Meibomian Gland Dysfunction. Photomed Laser Surg. 2018;36(6):326-32.
53. Shin KY, Lim DH, Moon CH, Kim BJ, Chung TY. Intense pulsed light plus meibomian gland expression versus intense pulsed light alone for meibomian gland dysfunction: A randomized crossover study. PLoS One. 2021;16(3):e0246245.
54. Yang L, Pazo EE, Zhang Q, Wu Y, Song Y, Qin G, et al. Treatment of contact lens related dry eye with intense pulsed light. Cont Lens Anterior Eye. 2022;45(2):101449.
55. Xu L, Wu Y, Song Y, Zhang Q, Qin G, Yang L, et al. Comparison Between Heated Eye Mask and Intense Pulsed Light Treatment for Contact Lens-Related Dry Eye. Photobiomodul Photomed Laser Surg. 2022;40(3):189-97.
56. Yan S, Wu Y. Efficacy and safety of Intense pulsed light therapy for dry eye caused by meibomian gland dysfunction: a randomised trial. Ann Palliat Med. 2021;10(7):7857-65.
57. Hovanesian JA, Berdy GJ, Epitropoulos A, Holladay JT. Effect of Cyclosporine 0.09% Treatment on Accuracy of Preoperative Biometry and Higher Order Aberrations in Dry Eye Patients Undergoing Cataract Surgery. Clin Ophthalmol. 2021;15:3679-86.
58. Shen Lee B, Toyos M, Karpecki P, Schiffbauer J, Sheppard J. Selective Pharmacologic Therapies for Dry Eye Disease Treatment: Efficacy, Tolerability, and Safety Data Review from Preclinical Studies and Pivotal Trials. Ophthalmol Ther. 2022;11(4):1333-69.
59. Efron N, Jones L, Bron AJ, Knop E, Arita R, Barabino S, et al. The TFOS International Workshop on Contact Lens Discomfort: report of the contact lens interactions with the ocular surface and adnexa subcommittee. Invest Ophthalmol Vis Sci. 2013;54(11):TFOS98-TFOS122.
60. Downie LE, Gad A, Wong CY, Gray JHV, Zeng W, Jackson DC, et al. Modulating Contact Lens Discomfort With Anti-Inflammatory Approaches: A Randomized Controlled Trial. Invest Ophthalmol Vis Sci. 2018;59(8):3755-66.
61. Fernandez I, Lopez-Miguel A, Martin-Montanez V, Enriquez-de-Salamanca A, Calonge M, Gonzalez-Meijome JM, et al. Inflammatory status predicts contact lens discomfort under adverse environmental conditions. Ocul Surf. 2020;18(4):829-40.
62. Toyos R, McGill W, Briscoe D. Intense pulsed light treatment for dry eye disease due to meibomian gland dysfunction; a 3-year retrospective study. Photomed Laser Surg. 2015;33(1):41-6.
63. Gupta PK, Vora GK, Matossian C, Kim M, Stinnett S. Outcomes of intense pulsed light therapy for treatment of evaporative dry eye disease. Can J Ophthalmol. 2016;51(4):249-53.

64. Yurttaser Ocak S, Karakus S, Ocak OB, Cakir A, Bolukbasi S, Erden B, et al. Intense pulse light therapy treatment for refractory dry eye disease due to meibomian gland dysfunction. Int Ophthalmol. 2020;40(5):1135-41.
65. Vigo L, Taroni L, Bernabei F, Pellegrini M, Sebastiani S, Mercanti A, et al. Ocular Surface Workup in Patients with Meibomian Gland Dysfunction Treated with Intense Regulated Pulsed Light. Diagnostics (Basel). 2019;9(4).
66. Lortie-Milner E, Boily L, Michaud L, Quesnel NM, Simard P, Milner V, et al. Translation and validation of the contact lens dry eye questionnaire 8 (CLDEQ-8) in Canadian French. Cont Lens Anterior Eye. 2023;46(2):101779.
67. Foulks G, Chalmers R, Keir N, Woods CA, Simpson T, Lippman R, et al. The TFOS International Workshop on Contact Lens Discomfort: report of the subcommittee on clinical trial design and outcomes. Invest Ophthalmol Vis Sci. 2013;54(11):TFOS157-83.
68. Chalmers RL, Keay L, Hickson-Curran SB, Gleason WJ. Cutoff score and responsiveness of the 8-item Contact Lens Dry Eye Questionnaire (CLDEQ-8) in a Large daily disposable contact lens registry. Cont Lens Anterior Eye. 2016;39(5):342-52.
69. Park J, Choi Y, Han G, Shin E, Han J, Chung TY, et al. Evaluation of tear osmolarity measured by I-Pen osmolarity system in patients with dry eye. Sci Rep. 2021;11(1):7726.
70. Chan CC, Borovik A, Hofmann I, Gulliver E, Rocha G. Validity and Reliability of a Novel Handheld Osmolarity System for Measurement of a National Institute of Standards Traceable Solution. Cornea. 2018;37(9):1169-74.
71. Chen Q, Wang J, Shen M, Cui L, Cai C, Li M, et al. Tear menisci and ocular discomfort during daily contact lens wear in symptomatic wearers. Invest Ophthalmol Vis Sci. 2011;52(5):2175-80.
72. Walker MK, Tomiyama ES, Skidmore KV, Assaad JR, Ticak A, Richdale K. A comparison of subjective and objective conjunctival hyperaemia grading with AOS(R) Anterior software. Clin Exp Optom. 2022;105(5):494-9.
73. Efron N, Morgan PB, Katsara SS. Validation of grading scales for contact lens complications. Ophthalmic Physiol Opt. 2001;21(1):17-29.
74. Pult H, Riede-Pult B. Comparison of subjective grading and objective assessment in meibography. Cont Lens Anterior Eye. 2013;36(1):22-7.
75. Binotti WW, Bayraktutar B, Ozmen MC, Cox SM, Hamrah P. A Review of Imaging Biomarkers of the Ocular Surface. Eye Contact Lens. 2020;46 Suppl 2(Suppl 2):S84-S105.
76. Tauber J, Schechter BA, Bacharach J, Toyos MM, Smyth-Medina R, Weiss SL, et al. A Phase II/III, randomized, double-masked, vehicle-controlled, dose-ranging study of the safety and efficacy of OTX-101 in the treatment of dry eye disease. Clin Ophthalmol. 2018;12:1921-9.
77. Tang Y, Liu R, Tu P, Song W, Qiao J, Yan X, et al. A Retrospective Study of Treatment Outcomes and Prognostic Factors of Intense Pulsed Light Therapy Combined With Meibomian Gland Expression in Patients With Meibomian Gland Dysfunction. Eye Contact Lens. 2021;47(1):38-44.
78. Chalmers RL, Begley CG, Moody K, Hickson-Curran SB. Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) and opinion of contact lens performance. Optom Vis Sci. 2012;89(10):1435-42.

79. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5(2):108-52.
80. Downie LE. Automated Tear Film Surface Quality Breakup Time as a Novel Clinical Marker for Tear Hyperosmolarity in Dry Eye Disease. Invest Ophthalmol Vis Sci. 2015;56(12):7260-8.
81. Gad A, Vingrys AJ, Wong CY, Jackson DC, Downie LE. Tear film inflammatory cytokine upregulation in contact lens discomfort. Ocul Surf. 2019;17(1):89-97.
82. Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. Clin Pharmacol Ther. 2014;95(6):617-26.
83. Armstrong RA. Statistical guidelines for the analysis of data obtained from one or both eyes. Ophthalmic Physiol Opt. 2013;33(1):7-14.
84. Schargus M, Ivanova S, Kakkassery V, Dick HB, Joachim S. Correlation of Tear Film Osmolarity and 2 Different MMP-9 Tests With Common Dry Eye Tests in a Cohort of Non-Dry Eye Patients. Cornea. 2015;34(7):739-44.