

Characterizing Contact Lens–Related Corneal Infiltrates: A Pilot Study

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Purpose: To document the time course and resolution of contact lens–related corneal infiltrative events (CIEs) comparing slit-lamp images with anterior segment ocular coherence tomography (AS-OCT) images.

Methods: Six silicone hydrogel (SiHy) soft contact lens (SCL) wearers presenting with newly diagnosed symptomatic CIEs were monitored with slit-lamp images, detailed drawings, and AS-OCT until the resolution of the CIE. A final follow-up visit was completed 4 weeks after CIE resolution to determine whether scar formation was present. Positive controls were 2 SiHy SCL wearers with established (inactive) corneal scars, and negative controls were 2 SiHy SCL wearers with clear corneas. High- and low-contrast logMAR visual acuities were measured, and subjective symptom questionnaires were completed at all visits.

Results: Clinical signs, vision, and symptoms improved in tandem with the resolution of the CIEs as measured by imaging methods. Calibrated measures of infiltrate width from a slit-lamp biomicroscope appear to be similar to calibrated images from AS-OCT.

Conclusions: Although further studies are needed to develop standardized procedures, AS-OCT can be a useful tool to characterize the development, progression, and resolution of corneal infiltrates as an objective measure of resolution and scar formation.

Key Words: corneal infiltrative events, corneal scarring, anterior segment OCT, contact lenses

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Corneal infiltrative events (CIEs) have become a growing concern for clinicians because of their increased incidence among contact lens wearers.¹ CIEs form from the gathering of leukocytes in the corneal tissue due to inflammation.² They can be asymptomatic or symptomatic and categorized as sterile or infectious by the clinician,^{3,4} often without any evidence from culturing. Previous research has proposed that CIEs can be categorized based on these characteristics,⁴ although this notion has been challenged.⁵

Known risk factors for CIEs include age (<25 years), ametropia, bacterial bioburden on eyelids, smoking, overnight soft contact lens (SCL) wear, and silicone hydrogel (SiHy) SCL material.^{6,7} They can often resolve without impact on the corneal tissue or visual acuity.^{4,8,9} However, they present with a range of severity, and in serious cases, they may lead to scarring and temporary or permanent reduction in visual acuity.^{1,4,8–10} Scar development from CIEs is poorly understood, and the course of infiltrate resolution has not been documented.^{1,10} Clinically, it may be difficult to differentiate CIEs from newly developed scars.⁴ Presently, slit-lamp biomicroscopy is the most commonly used method to monitor CIEs by documenting the size and location of the infiltrate,^{2,4,10} although details such as CIE depth are difficult to measure.^{11,12}

Optical coherence tomography (OCT) is a promising technique that has been previously used in the internal study of ocular tissues.¹³ The use of OCT is advantageous because it provides high-resolution, in situ, real-time imaging of internal structures in vivo without contact, using a noninvasive method.¹³ Anterior segment ocular coherence tomography (AS-OCT) has been used to study the morphology of the anterior segment of the eye, and thus this technology has been applied to the study of infiltrates in the cornea.¹⁴ AS-OCT provides imaging several micrometers deep and around 1 mm wide, allowing cross-sectional imaging of the corneal surface when compared with slit-lamp biomicroscopy.¹³

AS-OCT advances and software analysis may pave the way for the development of a novel objective method for evaluating CIEs. The purpose of this study was to prospectively document the time course and resolution of CIEs and explore the feasibility of using OCT imaging for characterizing the progression and resolution of contact lens–related CIEs, in hopes of developing a new evaluation method.

METHODS

This pilot study prospectively examined 6 habitual SiHy SCL wearers who presented to the Indiana University

(IU) Eye Care Clinics with a minimum of 1 active, symptomatic, focal infiltrate with either overlying corneal fluorescein staining and/or ≥ 1 mm in size in any direction. Two SiHy SCL wearers with established corneal scars (but no active disease) and 2 SiHy SCL wearers with no corneal opacities or active disease of similar age served as positive and negative controls, respectively. This study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The study was approved by IU Institutional Review Board.

Initial Visit

For infiltrate subjects, visit 1 took place on the day of initial presentation to IU clinic with symptomatic infiltrate/s. For scar and control subjects, visit 1 was scheduled in advance. After informed consent was obtained, history, demographics, and concomitant medication information were documented. The subject then completed subjective symptom questionnaires. Vision (with best correction) was assessed with high-contrast high-illumination and low-contrast high-illumination logMAR. Slit-lamp examination was conducted in which the clinician completed a detailed chair-side drawing including measured infiltrate/scar horizontal and vertical width for white light, sodium fluorescein staining, and lissamine green staining. Slit-lamp videos/photographs were also completed for all 3 scenarios. Corneal scans of the infiltrate region were obtained by the Visante AS-OCT Model 1000 (Carl Zeiss Meditec Inc). CCLRU grading scales were used to assess most clinical biomicroscopy signs.

Follow-up Visits

Subjects who presented with a corneal infiltrate had multiple follow-up visits. The clinician treating the infiltrate, independent of this study, determined a treatment regimen and frequency of clinical follow-up visits, as per clinical standard of care and outside the bounds of this study. Regardless of visit schedule, the infiltrate event was observed until resolution. For purposes of this study, event resolution was defined as completion of 2 consecutive visits with no active corneal findings. The final follow-up visit occurred 4 weeks after event resolution or approximately 6 weeks after initial presentation.

Subjects who were selected as controls with a corneal scar or with no active corneal findings had 1 additional observation study visit that occurred approximately 6 weeks after the first visit.

All follow-up visits included the same study procedures as the first visit.

Image Analysis

Corneal infiltrate depth, defined as the position of the posterior border of the infiltrate with respect to the corneal surface, was measured by AS-OCT caliper software at the time of testing, but the width was not. Custom Matlab (R2012b) program was used to reprocess raw AS-OCT image data, and image registration was performed for OCT image of each visit. Infiltrate width of OCT image was measured using ImageJ (v1.46r) software with calibrated scales after the completion of the study and compared with frames extracted from videos taken with the slit-lamp biomicroscope. Considering that suitable images with the AS-OCT and slit-lamp biomicroscope were not available for all of the infiltrates and scars, comparisons were performed on selected subjects whose images for both measurements were quantifiable.

Statistical Methods

Descriptive statistics for this pilot study were reported at baseline and each follow-up visit by subject and by subject group (infiltrate, previous scar, and no-scar controls). Continuous variables were summarized using sample size (n), mean, SD, median, minimum and maximum, and categorical data variables were summarized using the frequency count and percentage of subjects or eyes in each category.

An additional descriptive summary was completed to compare post hoc AS-OCT measurements of corneal infiltrates with measurements of the infiltrates from calibrated slit-lamp photographs.

RESULTS

Nine white participants and 1 Asian participant consisting of 8 women and 2 men completed the study. Six participants were included in the symptomatic CIE group, and 2 participants were included in each of the control groups.

TABLE 1. Number and Percentage of 6 Infiltrate Subjects Positive for Each Symptom at Each Visit

Symptom	Visit 1	Visit 2	Add V1	Add V2	Add V3	Add V4	Add V5
Pain/discomfort	6 (100)	2 (33.3)	1 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Itch	1 (16.7)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Blurry vision	4 (66.7)	6 (100)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Photophobia	6 (100)	5 (83.3)	2 (33.3)	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)
Dryness	2 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Discharge	4 (66.7)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection	6 (100)	5 (83.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased CL wear time	4 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Control and scar subjects had no symptoms present at visit 1 or visit 2.

"Add V1" through "Add V5" represent additional follow-up visits needed for infiltrate subjects for infiltrate resolution. The number of additional visits varied by subjects.

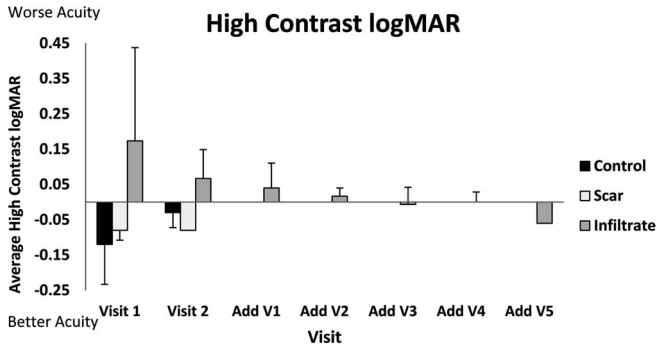


FIGURE 1. The average (\pm SD) high-contrast logMAR acuity for all study visits. Add V1-V5 denotes additional visits for the infiltrate group only.

The average age (\pm SD) was 21.9 ± 3.1 years. All subjects wore SiHy lenses. Subjects with corneal infiltrates were treated outside the confines of the study by doctors at the IU Eye Care Clinics.

Symptoms

Table 1 shows that all subjects in the infiltrate group reported pain and discomfort, photophobia, and injection on visit 1, with many also reporting discharge and blurred vision. These symptoms seemed to resolve by the second additional visit.

Visual Acuity

Subjects in the infiltrate group presented with poor visual acuity, which improved to near control levels by the end of the study (Figs. 1, 2).

Biomicroscopy

Horizontal and vertical infiltrate/scar size (width) was measured by the investigator while viewing infiltrates with a slit-lamp biomicroscope during some study visits (Fig. 3). In addition, infiltrate/scar depth was measured by the AS-OCT during data collection with caliper software (Fig. 4).

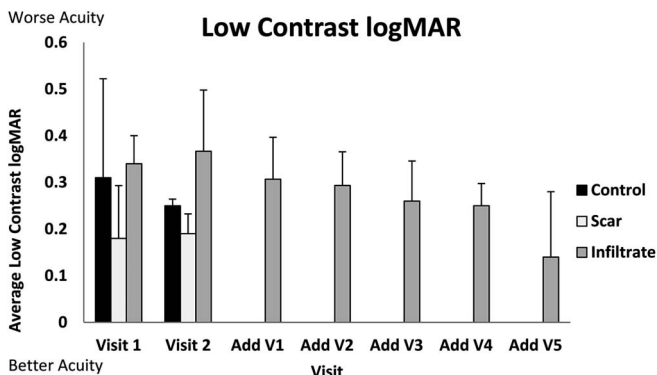


FIGURE 2. The average (\pm SD) low-contrast logMAR acuity for all study visits. Add V1-V5 denotes additional visits for the infiltrate group only.

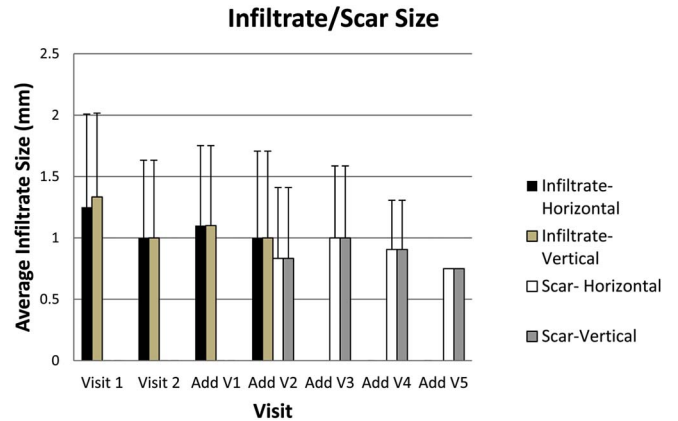


FIGURE 3. The average (\pm SD) horizontal and vertical infiltrate/scar size (mm) for infiltrate subjects as measured by the clinician at some study visits.

AS-OCT Additional Analysis

Not all AS-OCT or slit-lamp images were available or were of high enough quality to be analyzed by this method. Four of the 6 (67%) infiltrate subjects had usable AS-OCT measurements at most of their visits. The AS-OCT and slit-lamp images of 2 subjects' study visits revealed an infiltrative depth into the anterior stromal tissue as seen in Figures 5 and 6.

Early on, the infiltrate appeared to have rather indistinct margins; whereas once the scar was formed, the edges were more defined (Fig. 7). As expected, the scar formation also led to a marked decrease in symptoms.

DISCUSSION

Although slit-lamp biomicroscopy enables the visualization of corneal infiltrates and the determination of their size and location, it does not provide a way to objectively quantify the depth and stage of a CIE.^{11,12} Based on its use in the ocular system, AS-OCT may be used to provide more precise information on infiltrate depth, size, and stage. Thus, this study aimed to characterize and quantify the resolution of

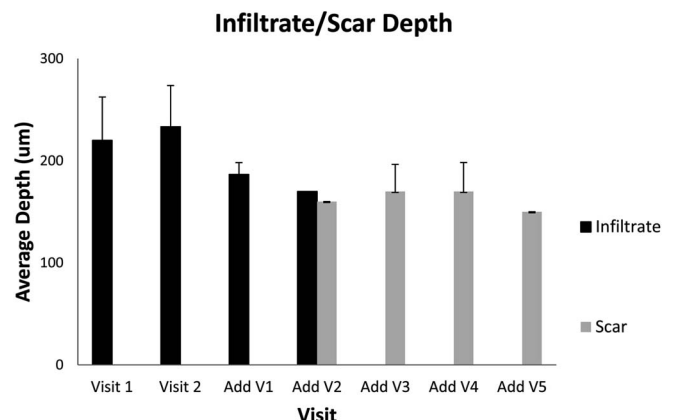


FIGURE 4. The average (\pm SD) depth of infiltrates/scars measured by AS-OCT caliper software (μ m) for infiltrate subjects at some study visits.

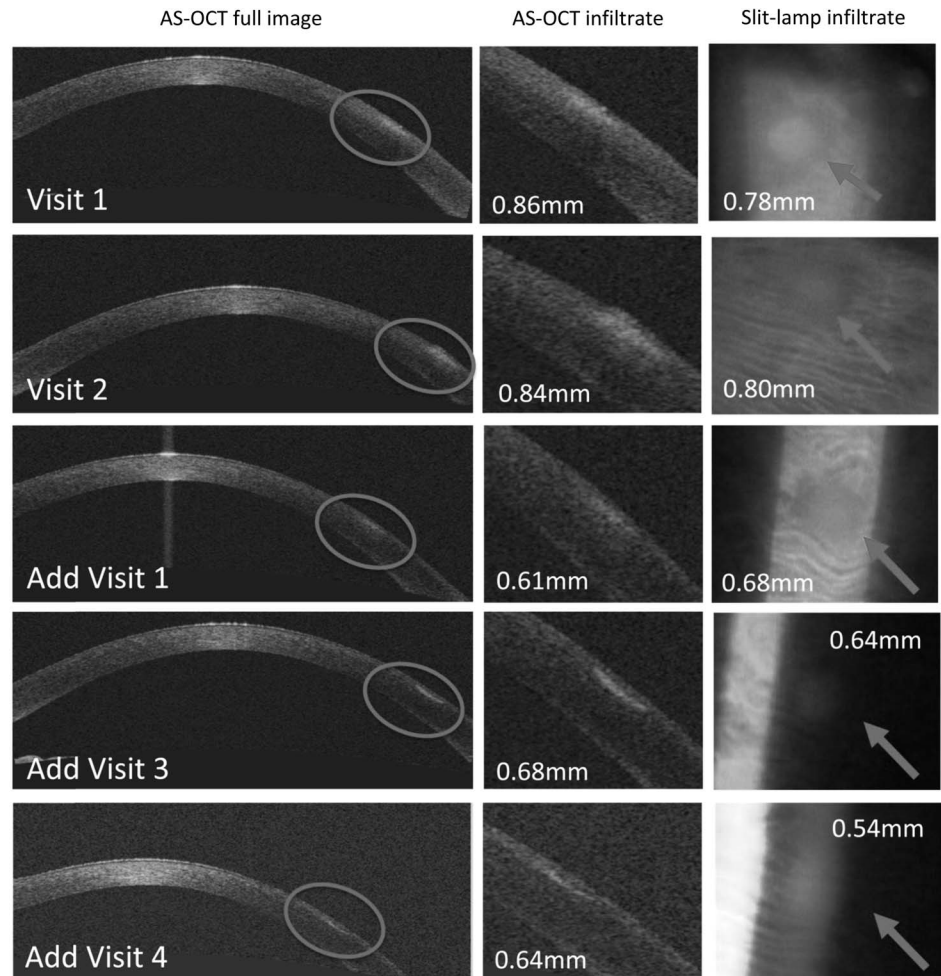


FIGURE 5. AS-OCT and slit-lamp biomicroscopy images from subject 8. Measurements are of infiltrate width with each method after calibration (AS-OCT images were missing from additional visit 2, but the slit-lamp measure of infiltrate width was 0.56 mm). Arrows and circles identify infiltrate location.

clinical signs and symptoms of CIEs through the use of clinician slit-lamp estimations, slit-lamp photograph measures, and AS-OCT as well as to determine the best methods for clinical grading and imaging of infiltrates. Clinical signs and symptoms were monitored during CIE resolution to determine whether there was a correlation between severity of symptoms and stage of infiltrate resolution. On presentation, all subjects with infiltrates reported symptoms often seen in CIEs, the most common of which were pain and discomfort, photophobia, and injection.^{15,16} In this study, infiltrate and symptom resolution were concurrent, and all symptoms were resolved by the end of the active CIE. Regarding injection associated with CIEs, Cook and Langham previously reported a decrease in vascularization and blood flow to thickened cornea after treatment of the infiltrative event, which may have been observed in this study.¹⁷ Pain and discomfort also decreased with infiltrate resolution which may be attributed to the decrease in inflammation and edema associated with infiltrate resolution.¹² However, considering that this study is the first to attempt to correlate symptom progression with infiltrate resolution, further studies are needed to support these findings. As seen in previous studies analyzing infiltrates, visual acuity resolved with the resolution of the infiltrate and there was no loss of visual acuity.^{4,9,18} Efron

et al⁹ reported that no significant difference in visual acuity could be detected between patients' eyes that had previously suffered a CIE and their unaffected eyes at a 27 ± 4 month follow-up visit. Baum and Dabezies observed that 20/20 visual acuity was reported after the resolution of sterile midperipheral corneal infiltrates.¹⁶ Furthermore, McClintic et al¹⁹ reported that visual acuity can continue resolution for 3 to 12 months after ulcer resolution due to ongoing scar improvement. Hence, it is necessary for regular follow-up visits to be scheduled after severe infiltrate resolution and scar formation to monitor the restoration of visual acuity.

In addition, this study monitored resolution time and reported an average of 9.9 (SD 5.5) days for infiltrate resolution. Aquavella and DePaolis²⁰ noted that while the acute phase of an infiltrative event may only last for 2 days, the infiltrate itself may take much longer to resolve. Josephson and Caffery²¹ suggested that there is a general correlation between severity and resolution time, such that more severe infiltrates take longer to resolve. Other studies have reported that contact lens-induced peripheral ulcers (CLPUs) and midperipheral infiltrates usually resolve within a week, whereas Sweeney et al reported that 1 to 3 weeks are needed for resolution.^{4,16} Considering that this study monitored active symptomatic infiltrative events, it is likely that

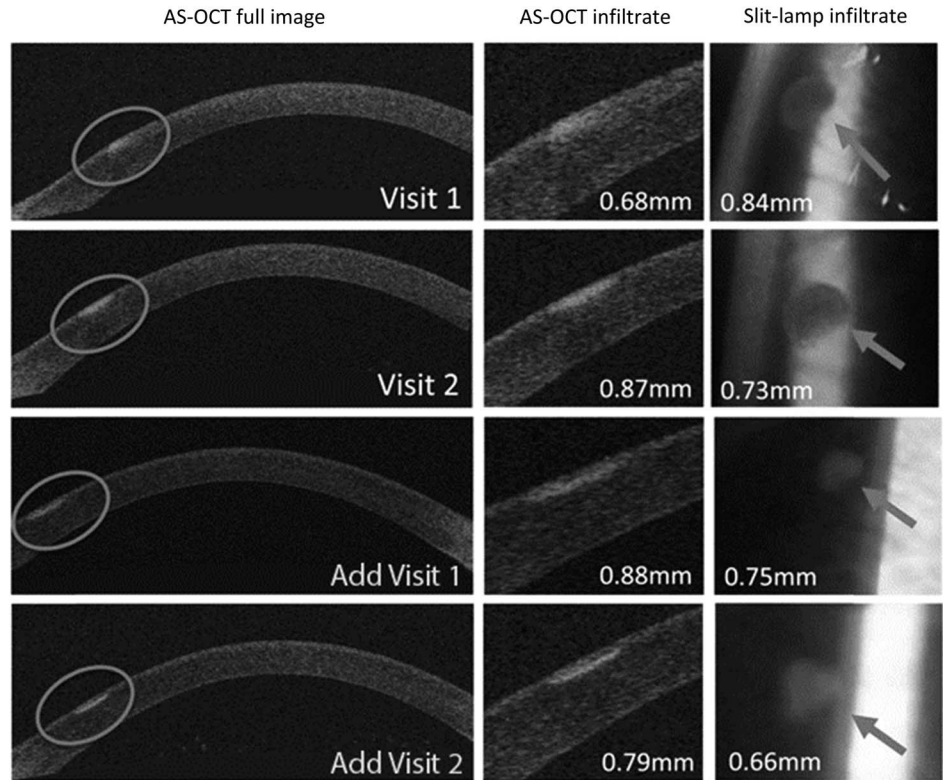


FIGURE 6. AS-OCT and slit-lamp bi-microscopy images from subject 9. Measurements are of infiltrate width with each method after calibration. Arrows and circles identify infiltrate location.

they were more severe than minor infiltrates, and more often associated with CLPU and therefore would take longer to resolve. More importantly, these findings indicate that there is a range of resolution times associated with corneal infiltrates, highlighting the need for more studies that monitor infiltrate resolution time.

Infiltrate depth is difficult to quantify and is usually subjectively determined by the clinician with the use of the

slit-lamp biomicroscope.^{11–14} Although previous studies measured corneal thickness, infiltrate thicknesses, and infiltrate width during resolution, the use of calipers provided with AS-OCT software alone resulted in a more subjective method of quantification.^{11,12} To use a less subjective and less manual measurement method, MatLab and ImageJ software were used, in addition to calipers, to determine the width and thickness of infiltrates and to monitor resolution and scar formation. As expected, changes in infiltrate depth and width were observed with infiltrate resolution. Konstantopoulos et al¹² reported similar results from a 14-day observation period in which the decrease in infiltrate thickness (depth) and corneal thickness with infiltrate resolution was attributed to the reduction of inflammation and edema over time. Interestingly, Konstantopoulos also reported infiltrative depth into the anterior stromal region¹² further demonstrating promise of the AS-OCT imaging. Yet, the depth of the infiltrate within the corneal tissue needs to be distinguished from the depth of the infiltrate itself. AS-OCT imaging (as shown in Figs. 5–7) reveals that infiltrative resolution can result in clear corneal tissue above the resulting scar. Nevertheless, depth of the infiltrates was measured from the anterior aspect of the cornea to the most posterior aspect of the infiltrate which is consistent with the previous literature.¹² Changes in infiltrate width, however, were hard to accurately quantify as Konstantopoulos et al indicated in their studies of infiltrate resolution.^{11,12} Indistinct infiltrate margins contributed to the difficulty in determining infiltrate width and are attributed to the great amount of corneal edema early in the inflammatory response.^{11,12,17} Furthermore, this study was consistent with previous ones in which margins became more distinct with

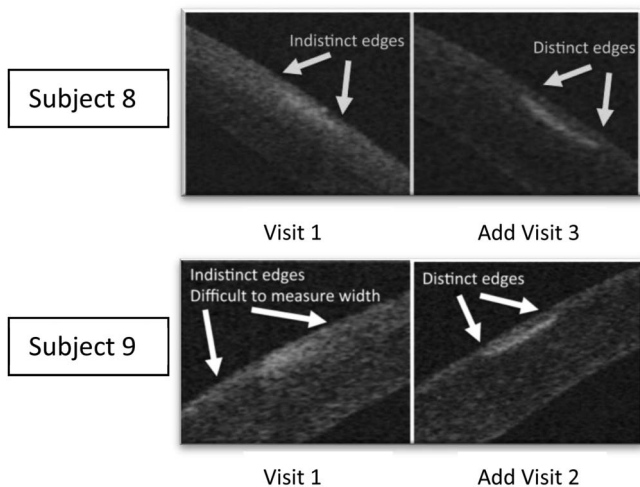


FIGURE 7. Enlarged AS-OCT images from subject 8 and subject 9 at visit 1 and additional visits showing changes in infiltrate edges over time that correspond with marked symptom improvement.

infiltrate resolution due to a reduction of corneal edema and inflammation.¹² The defined margins of the infiltrate are thought to be a precursor to clear resolution or scarring. Corneal scarring occurred in 5 of the 6 CIEs and did not seem to follow any certain trend or pattern in their formation. Minor scarring is often seen in CLPU and corresponds to the location of the infiltration.^{4,22,23} In infiltrative keratitis, scar formation may occur and is dependent on both infiltrate thickness and etiology.²⁴ Inflammation at the infiltrate location was associated with indistinct margins in both this study and previous ones.^{11,12} With infiltrate resolution, the reduction of inflammation and edema led to the ability to distinguish margins more clearly with the use of AS-OCT imaging.¹² From these findings, it is apparent that the clarification of infiltrate margins may indicate the stage of infiltrate resolution and scar formation. Because of the ability of AS-OCT imaging to aid in the distinction between corneal edema and infiltrate margins, it may be used to more accurately differentiate between active infiltrates and preexisting scars, leading to better treatment and diagnosis of CIEs.

Considering that this was a novel investigation, there are limitations associated with it. For instance, although it appeared that the sizes measured by calibrated slit-lamp photographs and AS-OCT were comparable, there was a discrepancy between clinician grading and software analysis of infiltrate size. Differences between subjective and objective grading are not uncommon as several metrics such as corneal staining, conjunctival hyperemia, and bulbar hyperemia reveal similar differences.²⁵ Rodriguez et al²⁵ reported that computer grading of ocular hyperemia was more reliable than the grading of another clinician. Similarly, Peterson and Wolffsohn²⁶ indicated that objective analysis of bulbar hyperemia was more sensitive to changes and reliable than subjective grading. Hence, it is not unexpected that differences between clinician size estimates and AS-OCT sizing were observed. Furthermore, the scale use for slit-lamp photographs and OCT measures was calibrated based on size of the pixel with magnification of the respective images, which would yield a more precise measure.

Because of the rather strict guidelines for entrance into the study (must be a new, active, symptomatic, and untreated infiltrate), recruitment took 13 months, which was much longer than anticipated. This accounted for the small sample size and lack of opportunity to study infiltrates with conventional hydrogel use, both limitations to this study. In addition, corneal scrapings were not taken so the etiology of the CIEs was not determined, leaving us unable to relate our findings to the specific CIE categories. Also, a learning curve was observed in the course of this study in the ability to scan the exact desired location of the cornea. More use of AS-OCT would aid the investigator in being able to better distinguish and capture the area of interest. Future studies may focus on determining a more reliable scanning method which would ensure the study of the same exact location at each visit. Future studies could also consider using confocal imaging along with AS-OCT images. Despite these limitations, the findings of this study align with the findings of previous more robust study designs, supporting these results and indicating their relevance to the existing body of knowledge.

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