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ORIGINAL ARTICLE

Risk Factors for Corneal Infiltrates with Continuous Wear of Contact Lenses

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ABSTRACT

Purpose. To describe the factors associated with symptomatic corneal infiltrates in a postmarket surveillance study of continuous wear contact lenses.

Methods. Patients intending to wear lotrafilcon A lenses continuously for 30 days and nights were registered in a 1-year study at 131 clinical sites. A self-administered questionnaire was used to gather demographic and other data at baseline. The severity of the incidence of corneal infiltrative events during the year-long study was graded by an independent adjudication committee.

Results. Of 6245 lens wearers, 163 were reported to have symptomatic corneal infiltrative events (2.6%). In 159 wearers, the infiltrates were judged to be lens-related (2.5%). Age ≤25 years and >50 years was significantly associated with the development of corneal infiltrates (≤25 years OR = 1.75, 95% CI = 1.24–2.48 and >50 years OR = 2.04, 95% CI = 1.40–2.98). Ametropia of ≥5.00 D was significantly associated with corneal infiltrates (OR = 1.60, 95% CI = 1.08–2.37). Study participants who typically wore lenses for >21 consecutive days and nights were significantly less likely to have infiltrates than those who wore lenses for fewer consecutive days and nights (OR = 0.43, 95% CI = 0.24–0.75). Smoking concurrent with contact lens wear was weakly associated with corneal infiltrates (OR = 1.47, CI = 0.99–2.18).

Conclusions. Patient age, degree of refractive error, and failure to achieve the intended wearing schedule were associated with development of symptomatic corneal infiltrative events.

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Key Words: silicone hydrogel lenses, corneal infiltrates, postmarket surveillance, risk factors

Corneal infiltrates associated with contact lens wear range in clinical presentation from small, peripheral, asymptomatic lesions limited to the corneal epithelium to central stromal ulceration with severe pain and loss of vision. Corneal infiltrates that resolve within a few days without treatment may initially appear very similar to those that will subsequently develop into more serious infections.[1,2] Therefore most practitioners treat such patients with topical antibiotics, as supported by published clinical guidelines and trials.[3–5] Conversely, in one study the role of microbes in mid-peripheral corneal infiltrates in contact lens wearers was tested by treating these eyes only with steroids.[1] That study showed that 88.9% of the presenting cases resolved without antibiotic treatment, indicating that many corneal infiltrates in contact lens wearers may be inflammatory rather than the direct result of microbial invasion.

We recently reported the rate of presumed microbial keratitis among wearers of a silicone hydrogel continuous wear contact lens (lotrafilcon A, CIBA Vision Corporation) based on this post approval surveillance study of 6245 wearers followed for 1 year; 10 patients of 6245 developed corneal lesions that were judged to be microbial keratitis.[6] However, during the course of that study, information was also collected on all symptomatic corneal infil-

trates occurring in the surveillance cohort. The purpose of this current analysis was to determine the demographic and refractive factors and patterns of lens usage that were associated with the development of symptomatic corneal infiltrates of any severity.

METHODS

Details of study methodology have been described previously.[6] Briefly, a total of 131 clinical practices that were actively dispensing NIGHT & DAY lenses (lotrafilcon A) for extended wear for up to 30 nights and days participated in the study. The practices were widely distributed geographically throughout the United States. Only patients intending to wear lenses continuously for up to 30 nights and days participated in the study. Previous self-reported contact lens history of participants included 39.4% daily wear, 37.6% extended wear, 9.5% NIGHT & DAY, 7.8% spectacles, 1.8% rigid gas permeable lenses, and 4% unreported. Spherical spectacle refraction ranged from +7.00 to −16.00 D. There was no restriction on refractive cylinder corrections. Contact lens power available at the time of the study ranged from +6.00 to −10.00 D. Table 1 summarizes key demographic factors for the enrolled population.

Patients completed a baseline survey in which demographic information and potential risk factors for microbial keratitis were obtained. The survey included questions on prior history of contact lens wear and typical wearing patterns. Clinicians completed a registration form that included contact lens prescription, spectacle refractive error, visual acuity, and preexisting ocular conditions. Questionnaires at 3 and 12 months queried typical wearing schedules, whether participants had discontinued lens wear, and the occurrence of a red or painful eye requiring a visit to an eye care or medical practitioner or an emergency room.

TABLE 1.
Wearer demographics and history of refractive correction at baseline

Wearer demographics	Number of wearers (%)
Gender	
Male	2259 (36.3)
Female	3977 (63.7)
Not reported	4 (0.06)
Age (yr)	
Average ± SD	34.8 ± 13.4
Range	5 to 86
Spectacle refraction (sphere only)	
Right eyes	
Mean ± SD	−3.21 ± 2.84
Range	−16.00 to +7.00
Left eyes	
Mean ± SD	−3.22 ± 2.88
Range	−13.75 to +6.50
Previous vision correction at baseline	
Soft hydrogel lenses	
Daily wear	2459 (39.4)
Extended wear	2347 (37.6)
Silicone Hydrogel lenses	
Continuous wear	591 (9.5)
Rigid gas permeable lenses	
Daily wear	92 (1.5)
Extended wear	20 (0.3)
Spectacles only	488 (7.8)
Not reported	248 (4.0)

Of the 6245 participants enrolled in the study, 4999 (80.0%) completed 12 months of lens wear; 893 (14.3%) discontinued lens wear before the 12-month survey completion (but with known outcome at the time of exit); 244 (3.9%) were lost to follow-up after completing the 3-month survey; and 109 (1.7%) did not complete a 3- or 12-month survey.

Lens wearers with potential corneal infiltrates were initially identified by their positive responses to the question about red or painful eye in the 3- and 12-month surveys. Cases were also actively reported by registration centers if the wearer returned to that practice for treatment of the infiltrate. The complete medical records of all cases with possible corneal infiltrates were requested. All cases with documentation of a corneal infiltrate were graded for severity by the Endpoint Adjudication Committee, according to preestablished guidelines.[7]

The incidence rate for subjects experiencing at least one symptomatic infiltrate during the period of the study was calculated by dividing the number of persons experiencing at least one infiltrate case by the number of enrolled subjects. The association of baseline risk factors with development of at least one infiltrate was assessed individually in a bivariate analysis and those factors with p values <0.10 were included in a multivariable logistic regression model [adjusted odds ratio (OR)]. Factors that were significant in the multivariate model were then tested in a bivariate analysis to determine association with infiltrate severity. Gender was included in all models even though there was no bivariate association because of its association in previous studies.

Because high ametropia has been shown to be related to infiltrate incidence in other studies,[7,8] baseline data for low and high ametropes (absolute refractive error greater than or equal to 5.00 D sphere) was analyzed in an exploratory fashion to test for baseline differences in contact lens history and associated behaviors between low and high ametropes.[7–9] The differences in baseline responses between high and low ametropes were analyzed by chi-square test and are described in the results. Because of small numbers for some of the responses, this subanalysis was not of sufficient power to determine the role of these factors in the development of infiltrates for these groups.

Because of the unequal contribution of lens wearers per clinical site, we did not include clinical site as a factor in the multivariate analysis. Because of the potential correlation of outcomes by clinic site, logistic regression models were fit using Generalized Estimating Equations with a logit link and exchangeable correlation structure.[10] This was done for the crude ORs for individual risk factors as well as for the multivariate logistic regression. A separate analysis was performed to determine the correlation between number of subjects enrolled at a site and the rate of infiltrates reported at that site.

RESULTS

One hundred sixty-three (2.6%) lens wearers experienced 183 symptomatic corneal infiltrates of varying severity and in 159

TABLE 2.
Distribution of severity of confirmed infiltrative events

	Number of wearers
Contact lens related	159
Level 1: High probability of microbial keratitis with loss of vision	2
Level 2: High probability of microbial keratitis without loss of vision	8
Level 3: High probability of infiltrative keratitis of indeterminate etiology	52
Level 4: High probability of sterile infiltrative keratitis	97
Not contact lens related or can't tell	4
Level 5: High probability of infiltrative keratitis *not* related to lens wear	2
Can't tell, but not level 1 or 2	2
Total	*163*

Some wearers experienced more than one Level 3, 4 or 5 events.

(2.5%) wearers the infiltrates were judged to be lens related. Table 2 contains the distribution of infiltrates by severity level.

Contact lens wearers with confirmed infiltrative events were attributed to 66 of the 131 clinical sites in the study. Patients with infiltrates were not proportionally distributed across clinical sites; the incidence of infiltrates per clinical site ranged from 0 to 14.3% ($p = 0.008$, $\chi^2 = 180.0$). Incidence of corneal infiltrative events per clinical site was not significantly correlated with the number of subjects enrolled at that site ($r = 0.09$, $p = 0.30$, Pearson's correlation).

The results of the multivariate analysis are shown in Table 3. These factors were also tested for their role in severity of infiltrates, the results of which will be described individually for each factor.

Wearing Schedule

Wearing the lens continuously for more nights and days was significantly associated with a lower risk of developing an infiltrate. In this study, a reported typical overnight wearing schedule of 3 week or more of continuous wear was associated with a significantly lower rate [0.43, 95% confidence interval (CI) = 0.24–0.75] of corneal infiltrates compared with reported daily wear schedule during the study period. A shorter wearing schedule was also significantly associated with increased severity of events ($\chi^2 = 21.7$, $p = 0.01$).

Demographic Factors

Wearers who were at the younger and older ends of the age distribution had a significantly higher risk of developing infiltrates. Wearers 25 years of age and younger had a 3.2% prevalence of infiltrates and a 1.75 times higher risk of infiltrates (95% CI = 1.24–2.48) compared with those between 26 and 50 years (Fig. 1).

TABLE 3.
Odds ratios and per wearer incidence of infiltrates by risk factor

Factor	Number of noncases	Number of cases	Incidence (%)	Crude odds ratio[a] (95% CI)	Adjusted odds ratio[a] (95% CI)
Age (yr)					
≤25	1691	56	3.2	**1.66 (1.19–2.32)**	**1.75 (1.24–2.48)**
26–50	3498	69	1.9	**1.00**	**1.00**
>50	894	32	3.5	**1.86 (1.30–2.64)**	**2.04 (1.40–2.98)**
(5 missing)					
Spectacle Rx (Absolute sphere)					
<5.00 D	4565	106	2.3	1.00	1.00
≥5.00 D	1518	51	3.3	1.40 (0.97–2.03)	1.60 (1.08–2.37)
(5 missing)					
Overnight wear					
None (daily wear)	269	12	4.6	1.00	1.00
1–6 nights	610	23	3.6	0.76 (0.42–1.35)	0.72 (0.40–1.30)
1–2 weeks	649	22	3.3	0.67 (0.36–1.27)	0.70 (0.37–1.32)
≥3 weeks	4426	98	2.2	**0.44 (0.26–0.76)**	**0.43 (0.24–0.75)**
(135 missing)					
Current smoker					
No	5112	124	2.4	1.00	1.00
Yes	885	30	3.3	1.40 (0.94–2.08)	1.47 (0.99–2.18)
(94 missing)					
Gender					
Female	3874	103	2.6	1.00	1.00
Male	2211	53	2.3	0.88 (0.62–1.25)	0.86 (0.60–1.23)
(4 missing)					

Only wearers with available data are analyzed. Significant factors listed in bold.

[a]Crude and adjusted odds ratios account for correlation of cases by clinic using Generalized Estimating Equations with a logit link and exchangeable correlation structure.[10]

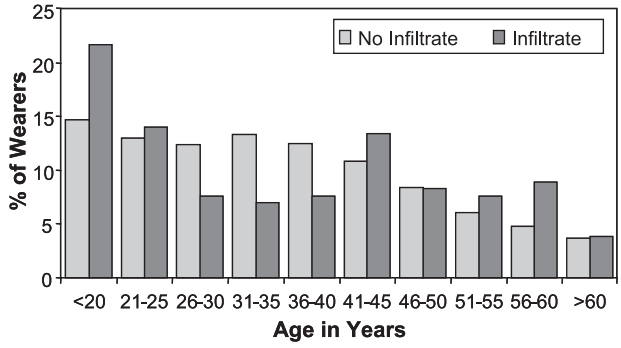

FIGURE 1.

Frequency distribution of age of lens wearer for lens wearers with and without corneal infiltrative events. (Light gray bars = lens wearers without corneal infiltrative events; dark gray bars = lens wearers with corneal infiltrative events.)

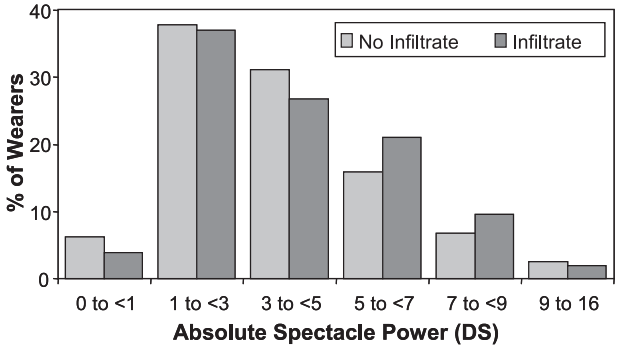

FIGURE 2.

Frequency distribution of ametropia (absolute sphere power) for lens wearers with and without corneal infiltrative events. (Light gray bars = lens wearers without corneal infiltrative events; dark gray bars = lens wearers with corneal infiltrative events.)

Lens wearers who were older than 50 years had 3.5% prevalence of infiltrates and a 2.04 times higher risk of infiltrative events (95% CI = 1.40, 2.98) compared with the 26 to 50 year age group. The older and younger age groups accounted for 56% of all wearers with corneal infiltrative events and 43% of those without. Youth or older age were also significantly associated with the severity of infiltrates; 8 of 10 subjects with the most severe infiltrates were outside the 26 to 50 year age group ($\chi^2 = 15.5$, $p = 0.017$).

Gender was not a significant demographic factor for the development of infiltrates in this study (males OR = 0.86, 95% CI = 0.60–1.23). There was a trend for an association between male gender and infiltrate severity; 60% of the wearers with level 1 and 2 infiltrates were males compared with 32% males among those with less severe events ($\chi^2 = 7.32$, $p = 0.062$).

Current smoking was associated with an OR of 1.47 (95% CI = 0.99–2.18) in the multivariate model, but was not a significant factor.

Corneal scars were present at baseline in 3.3% of the patients who developed infiltrates during the year of observation and in 1.5% of those who did not develop infiltrates. This difference was not significant ($\chi^2 = 3.06$, $p = 0.08$).

Another variable that was associated with the risk of an infiltrate in the bivariate analysis was a history of a contact lens related problem for which medical care was sought within the year before enrollment in the study (crude OR = 1.65, 95% CI = 1.04–2.62). However, this question was only asked of the subset of participants who were prior contact lens wearers (n = 6064). When adjusted for age, sex, spectacle correction, smoking and wearing schedule, this risk factor was no longer statistically significant (adjusted OR = 1.48, 95% CI = 0.94–2.34) although it was significantly associated with development of infiltrates of greater severity ($\chi^2 = 8.91$, $p = 0.03$). The final regression model did not include this variable.

Degree of Refractive Error

High Ametropia. As shown in Fig. 2, wearers with spectacle refractive errors above ±5.00 D ("high ametropes") were 1.60 times more likely to present with an infiltrate during the study (3.3% vs. 2.3%: CI = 1.08–2.37). High ametropia was also significantly associated with increasing severity of infiltrates ($\chi^2 = 8.26$, $p = 0.04$).

A comparison of baseline questionnaires for high and low ametropes showed significant differences in numerous factors with their habitual vision correction. High ametropes reported longer years of contact lens wear at baseline compared with low ametropes, with 32.5% of them reporting > 20 years of wear compared with 16.4% of the low ametropes ($\chi^2 = 442.0$, $p = 0.0001$). A lower percentage of high ametropes reported owning a satisfactory pair of spectacles, and they owned spectacles that were older on average (own spectacles $\chi^2 = 4.35$, $p = 0.037$ and age of spectacles $\chi^2 = 7.9$, $p = 0.048$).

At baseline the high ametropes were significantly more likely to report contact lens related symptoms of red eyes, dryness in the morning and at night, and uncomfortable lenses on insertion (red eyes $\chi^2 = 39.6$, $p = 0.0001$; dryness in morning $\chi^2 = 16.6$, $p = 0.0001$; dryness at night $\chi^2 = 11.1$, $p = 0.0008$; discomfort on insertion $\chi^2 = 5.6$, $p = 0.018$). They also reported less frequent rewetting drop usage at baseline ($\chi^2 = 7.88$, $p = 0.049$).

High ametropes also exhibited more ocular health problems with their previous lenses. Baseline corneal neovascularization was noted by registering clinicians in 13.2% of the high ametropes compared with 5.9% of the low ametropes ($\chi^2 = 84.7$, $p = 0.0001$). At baseline the high ametropes had a history of more frequent corneal abrasions, more clinical visits related to having red eyes, a higher incidence of giant papillary conjunctivitis (GPC) and more occurrence of lens deposits than the low ametropes (abrasions $\chi^2 = 21.6$, $p = 0.0001$; red eye visits $\chi^2 = 4.8$, $p = 0.03$; GPC $\chi^2 = 17.4$, $p = 0.0001$; deposits $\chi^2 = 43.7$, $p = 0.0001$).

DISCUSSION

In this article, the incidence of symptomatic corneal infiltrates in the open clinical marketplace has been measured and risk factors associated with their development have been analyzed. The prospective study design employed here has the primary limitation of studying wearers of only one lens type, the lotrafilcon A lens, which may impact the ability to generalize the results to other silicone hydrogel lenses now in clinical use. The study registered patients in the U.S. who purchased lenses in many general eye care practices

and it began within the first year of FDA approval for up to 30 nights continuous wear of these lenses. Thus, the patients registered in this study during this early phase of marketing may represent a self- or practitioner-selected group which is at somewhat higher risk than those using the product after several years in the marketplace, or those who are chosen for prospective clinical trials in research centers. Those factors and other differences in study design may explain the slightly higher incidence of lens related infiltrates found here (2.5%) compared with that reported for silicone hydrogel lenses in other studies, such as the 1.2% reported by Efron and co-workers in the UK.[11] The infiltrate rate in this study was very consistent with that found in registration trials with the lotrafilcon A lens. The stability of rates validates that the open market use of the lens was robust to the multitude of factors presented in the open clinical setting after regulatory approval.[8]

The primary advantage of the prospective study design is the provision of a stable control group—those wearers who did not experience infiltrates—against which to compare the wearers who developed infiltrates during the year long study. Through use of an extensive self-administered baseline questionnaire, the study was able to gather information on a large number of potential risk factors that had been mentioned in previous case series and other reports. These factors were implicated as drivers for corneal inflammation, but had not been verified as risk factors in large prospective studies or with silicone hydrogel lenses in particular. In addition, with a registered cohort approach we obtained full information on the refractive correction of all patients, a significant factor in the risk of experiencing a corneal infiltrative event. The study of refractive error as a risk factor would not be possible in population based study designs, as individuals rarely know their spectacle prescription with any precision.

Our study was not able to reveal the effect of practitioner choices in terms of patient selection or prescribed care and use instructions. Although we found a very large range of incidence across the clinical sites, from 0% to 14.3%, it was not significantly correlated, either positively or negatively, with the number of participants enrolled per site. This is not to say that sites with more registered wearers had the highest incidence of infiltrates; in fact the site with the highest rate enrolled only seven participants in the study. The use of direct mail and telephone contact with the registered lens wearers to gather potential events reduced the impact of varying practitioner compliance with reporting events. The clinical center was included as part of our multivariate model to control for clustering effects caused by clinical site or prescribing habits.

In this study the lens wearer's age was a significant factor in the development of infiltrates, both at the younger and older end of the age scale. Younger age has previously been reported as a significant risk factor for infiltrates[8,12] and for microbial keratitis with contact lens wear[13] We found increased risk among older lens wearers as well. Although a study of this type is unable to establish the cause for increased risk, either behavioral or biological factors common to or specific to those age groups may be probable causes.

Teens and young adults also often admit to lifestyle practices that they know compromise their health[14,15] and the safety of their contact lens wear in particular.[16] To illustrate the point, in this study, some of the more severe events began with a call to the prescribing practitioner from a parent of an older teen or young adult who was away at college. Very often these patients delayed proper professional management of their problem by days because of their inexperience in self-management of their own health care. However, studies have shown that college students actively seek health information and simple interventions that offer self-care information to college students can change attitudes about their active participation in managing their health care.[17,18]

The relationship between patient age and ocular flora is a possible factor in the increased risk of infiltrates for patients at the younger and older end of the age spectrum. Inadequate hygiene among teens and older patients may increase the lid flora of bacteria associated with the development of infiltrates. In a large prospective study with hydrogel lenses, colonization of the lens surface by S *pneumoniae* on the lens surface was a significant factor in the development of corneal infiltrates in a large prospective study with hydrogel lenses.[19] The presence of S *pneumoniae* appeared specific to the lens surface as the organism was not found in large numbers in conjunctival or lid samples. One can postulate that the use of contact lenses on an overnight basis may keep some bacterial byproducts in contact with the corneal surface for a longer period of time, thus leading to a corneal infiltrative response. Another finding that supports the idea that the patients' ocular flora may have a role in the development of infiltrates with lenses is the significant association with previous emergency visits and corneal scars that may be related to immune reactions from lid flora.

Older contact lens wearers may have other concomitant ocular surface conditions that could contribute to the development of infiltrates, such as blepharitis and dry eye which are thought to occur more often with advancing age.[20,21] However, when blepharitis is present in children or teens it is also stubborn and difficult to control.[22] This study did not find a significant association between blepharitis or dry eye and the development of infiltrates, limited possibly by the small numbers reporting it as a prior condition by the registering investigators. Morgan and co-workers also found that eye disease in general was associated with a lower risk of developing infiltrates and they proposed that it may be due to more careful lens wearing behaviors among patients who have concomitant disease.[13]

In this study, wearing the lens continuously for >21 nights and days was associated with a decreased risk of infiltrates. The group without corneal infiltrates had a longer average period of continuous wear. However, only patients who desired and intended to pursue a wearing schedule of continuous wear up to 30 nights were registered in the study. After enrollment, participants could subsequently have adapted their wearing schedule because of any number of factors, such as visual demands, comfort problems, practitioner recommendation, personal motivation, or ocular surface symptoms. It is indeed possible that the shorter wearing schedules were a result of experiencing problems and are not a direct or indirect cause of the problems. Because of all these confounding variables, it is not possible to determine the degree to which continuous night and day wear, per se, has impacted the outcome in this study. A randomized trial where subjects are assigned to varying wearing schedules would be required to determine whether longer or shorter wearing times were associated with the development of corneal infiltrates.

Ametropia of 5 D or greater was a significant ocular risk factor for infiltrates in this large study and in a previous registration trial

with balafilcon A silicone hydrogel lenses.[9] High ametropes who had been using hydrogel lenses in this study presented at baseline with features that were significantly different from their low ametropic counterparts: more corneal scars, more corneal neovascularization, more ocular surface symptoms, and a longer history of contact lens wear. They also were more likely to report having had an office visit that related to a red or painful eye in the past compared with the low ametropes. The impact of these differences between low and high ametropes may well contribute to the difference in risk for corneal infiltrates with lens wear and be factors that can be influenced by counseling or informing the patient of their added risk.

In a cross-sectional study of 2161 hydrogel contact lens wearers, Zadnik et al. found that ametropes above 5.00 D had significantly greater corneal fluorescein staining, neovascularization and scars, and that they exhibited different self-management behaviors compared with the low ametropes.[23] High ametropes in that study were more likely to keep wearing their hydrogel lenses after onset of a symptomatic infiltrate and performed more extensive self-management when they experienced corneal infiltrates. These behavioral factors may represent an increased amount of dependence on contact lenses among the high ametropes. In support of their dependence on contact lenses, we found that high ametropes had glasses that were older and less satisfactory. Owning spectacles that are not up to date in terms of refractive correction or style could discourage a lens wearer from removing lenses when a problem arises. Other lens related factors such as power-related differences in the physical properties (e.g., thickness, stiffness) of contact lenses across the power range may also impact the higher rate of infiltrates seen among those with >5 D ametropia in this and the earlier studies.

Other risk factors that differed from the work of Morgan and Efron in the UK[11,12] are the lack of significance for current smoking and male gender in this study. Current smoking did trend strongly toward significance (adjusted OR 1.47;CI = 0.99–2.18) and was likely limited only by the lower proportion of smokers in the US cohort (14.9%).

CONCLUSIONS

The 2.5% per wearer annual incidence of corneal infiltrates in this post approval study of lotrafilcon A lenses was similar to that found in premarket trials of the lenses when used on an up to 30 night continuous wear basis, further confirming the safety and effectiveness in real-world clinical practice.[8] The average rate of corneal inflammatory responses with continuous wear of lotrafilcon A lenses remained unchanged when prescribed in the less rigid setting studied here.

Patient age and degree of refractive error were significantly associated with the risk of developing a corneal infiltrate in this year-long study. Lens wearers ≤25 years and >50 years of age had a higher risk of infiltrates, as did ametropes of 5 D or more. Paradoxically, lens wearers who achieved and maintained the continuous overnight wear schedule that was prescribed at the beginning of the study had lower risk compared with those wearers who reported shorter duration continuous wearing schedules during the trial. A shorter wearing schedule, however, may be an outcome rather than a risk factor. Neither current smoking nor male gender was a significant risk factor for corneal infiltrates in this study, although both of them showed a trend toward significance.

Patients with high amounts of ametropia presented for the study with many significant differences in their lens wearing history and habits, including longer years of wear, not owning current spectacles and coping with a higher rate of symptoms and problems with their lenses. These factors, although not tested directly here, may contribute to the high ametropes' higher risk of developing infiltrates with continuous lens wear. High ametropes should be encouraged to own a current pair of spectacles to better manage early symptoms of corneal inflammation by removing their contact lenses while they seek professional care.

This study demonstrates the clinical acceptability of continuous wear with silicone hydrogels and highlights factors that play a role in their successful wear. Clinicians now have guidance to help in an individualized approach to choose the best lenses and wearing schedules for each patient based on their demographic and refractive profile. Assessment of the presence of risk factors for various types of patients could be helpful in counseling them before they embark on continuous wear.

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