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Research article

Effect of antihistamine-releasing contact lenses on ocular symptoms and treatment behavior in patients with seasonal allergic conjunctivitis: A retrospective study

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ABSTRACT

Purpose: This study aimed to compare subjective allergic conjunctivitis symptoms and anti-allergic eye drop use patterns between antihistamine-releasing contact lens users and daily disposable soft contact lens users during Japan's hay fever season.
Methods: This web-based retrospective cohort study included daily disposable soft contact lens or antihistamine-releasing contact lens users with a history of seasonal allergic conjunctivitis who regularly used daily disposable soft contact lenses since the previous year. The total ocular

Abbreviations: ARCL, antihistamine-releasing contact lens; CL, contact lens; CLPC, contact lens-induced papillary conjunctivitis; DSCL, daily disposable soft contact lens; SAC, seasonal allergic conjunctivitis; SCL, soft contact lens; TOSS, total ocular symptom score.

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symptom score (range 0–20) based on 5-item questionnaire scores and time from the start of the hay fever season to the initiation of anti-allergic eye drop treatment were compared between antihistamine-releasing contact lens users and daily disposable soft contact lens users.
Results: The study included 24 participants: 17 using daily disposable soft contact lenses and 7 using antihistamine-releasing contact lenses. Antihistamine-releasing contact lens users experienced a greater reduction in total ocular symptom score from 2021 to 2022 compared with daily disposable soft contact lens users (mean total ocular symptom score [standard deviation]: daily disposable soft contact lens: −0.65 [1.4], antihistamine-releasing contact lens: −4.7 [3.6]; n = 24; Mann–Whitney *U* test, $P = 0.010$). Fourteen daily disposable soft contact lens users and five antihistamine-releasing contact lens users eventually required anti-allergic eye drops. Kaplan–Meier analysis revealed a significant delay in the initiation of anti-allergic eye drop treatment among those using antihistamine-releasing contact lenses compared with those using daily disposable soft contact lenses (median days, daily disposable soft contact lenses: 19 days, antihistamine-releasing contact lens: 57 days; n = 24; log-rank test, $P = 0.045$).
Conclusions: Antihistamine-releasing contact lenses can potentially mitigate worsening ocular allergic responses during the hay fever season when used appropriately as a preventive measure.

1. Introduction

Hay fever is highly and increasingly prevalent and estimated to affect approximately 25 % of the global population [1,2]. Patients with seasonal allergic conjunctivitis (SAC) and rhinitis related to hay fever present with a wide range of symptoms and severity that are detrimental to their quality of life and work productivity [3–5]. Notably, ocular irritation and increased lacrimation due to SAC frequently cause eye discomfort during contact lens (CL) use and are common reasons for CL discontinuation during symptomatic periods [6,7]. Moreover, CL use is a risk factor for the development of CL-induced papillary conjunctivitis (CLPC), a subtype of giant papillary conjunctivitis. CLPC is triggered by two factors: 1) the formation of a lipid- and protein-heavy biofilm on the CL surface, making it susceptible to bacterial growth, and 2) the physical friction between the anterior surface of the CL and the palpebral conjunctiva [8,9]. Additionally, the decreased tear circulation ("turnover") on the ocular surface and CL-induced allergic response brought on by prolonged CL use aggravate SAC during high-pollen seasons [10]. Therefore, particularly for regular CL users, aggressive preventive measures and treatment regimens are essential when managing SAC in anticipation of an approaching hay fever season.

ACUVUE® Theravision® with ketotifen (AllerCare® in certain regions) released by Johnson & Johnson (MA, USA) is an etafilcon A-based single-use CL best known for being the world's first official antihistamine-releasing CL (ARCL) containing ketotifen fumarate [6]. In a conjunctival allergen challenge trial conducted by Pall et al. where participants were randomly assigned to ARCL and placebo groups, ARCL users reported a statistically significant decrease in subjective ocular irritation in eyes compared with those in the placebo group when the allergen challenges were performed at 15 min and 12 h after initial CL placement [6]. Following subsequent trials, ACUVUE® Theravision® was formally approved in Japan in March 2021 as the first soft contact lens (SCL) capable of releasing antihistamine during use [9]. While ACUVUE® Theravision® may not be appropriate as *post facto* treatment of SAC symptoms, such as ocular irritation, its potential for SAC prevention when initiated before allergen exposure during hay fever season appears promising. Although the effectiveness of ARCL use for SAC has been reported in a few case reports [9,11], a formal appraisal of the subjective symptoms of SAC during ARCL use and its subsequent effects on ocular treatment patterns has not yet been conducted.

Therefore, this study aimed to compare subjective symptoms of allergic conjunctivitis and anti-allergic eye drop use patterns in ARCL and daily disposable SCL (DSCL) users during Japan's hay fever season when high cedar and cypress pollen dissemination is observed.

2. Materials and methods

2.1. Study design and participants

This web-based retrospective cohort study was conducted between January 4, 2022, and May 31, 2022, and approved by the Independent Ethics Committee of Juntendo University Faculty of Medicine (approval number: E21-0220-H01). This study adhered to the tenets of the Declaration of Helsinki. Electronic informed consent was obtained from all participants. Participants completed all questions using the mobile communication tool LINE (LINE Corporation, Tokyo, Japan) and received an Amazon gift certificate worth 500 yen.

The inclusion criteria were as follows: age ≥20 years; history of hay fever due to cedar or cypress pollen; history of using anti-allergic eye drops every year (history of SAC); using ARCLs or DSCLs at the time of the survey; and regularly using DSCL for at least 8 h a day, 5 days a week since the previous year. Conversely, patients with active allergic conjunctivitis based on in-person examination by a physician or those actively using anti-allergic eye drops at the time of the study were excluded.

We defined the hay fever season as February to May when cedar and cypress pollen allergy rates increase in Japan due to the increased dispersion of both pollens [2,12].

2.2. Study procedures

Fig. 1 illustrates the study procedure. This web-based retrospective cohort study was conducted using LINE, the most frequently used mobile communication tool in Japan [13]. Patients were recruited at clinics to register with the official LINE account of the study's host department between January 4 and January 31, 2022 (Fig. 1a). We confirmed the inclusion criteria with patients with SAC by in person interview by a physician and excluded patients with active allergic conjunctivitis based on the ocular findings or those actively using anti-allergic eye drops at the time of visit. In this study, the contact lens type was voluntarily selected by the participants, and allocation between the ARCLs or DSCLs groups was not performed. Subsequently, after the peak pollen dispersal in Japan [2], from May 9 to May 31, 2022, survey uniform resource locators were shared with registered patients via LINE (Fig. 1b). After obtaining patient consent on the linked web page (Fig. 1c), participants completed the survey using Google Forms (Google LCC, Mountain View, CA, USA) (Fig. 1d).

2.3. Web questionnaire format

Participants completed a web-based survey using Google Forms to investigate subjective ocular hay fever symptoms and the use of anti-allergy eye drops during the hay fever season in Japan (Fig. 2a). The questionnaires are presented in Supplementary Table 1. Data on demographic characteristics, medical history, lifestyle, CL details, subjective ocular symptoms for hay fever in the previous and current year, and use of anti-allergic eye drops and anti-allergic oral medication were collected (Fig. 2b).

2.4. Subjective ocular symptoms of hay fever

Ocular symptoms during the hay fever season for 2021 and 2022 were quantified using a 5-item questionnaire, including the items on eye symptoms in Domain I of the Japanese Allergic Conjunctival Disease Standard Quality of Life Questionnaire (JACQLQ), such as itchy eyes, foreign body sensation, red eyes, watery eyes, and eye discharge [14]. The reliability and validity of the digital administration of the JACQLQ have been proven in previous studies [15,16]. The degree of subjective ocular symptoms was assessed on a 5-point scale (no symptoms, mild, somewhat severe, severe, and very severe, 0 to 4 points). The total ocular symptom score (TOSS) was calculated by adding each score (score range; 0–20 points).

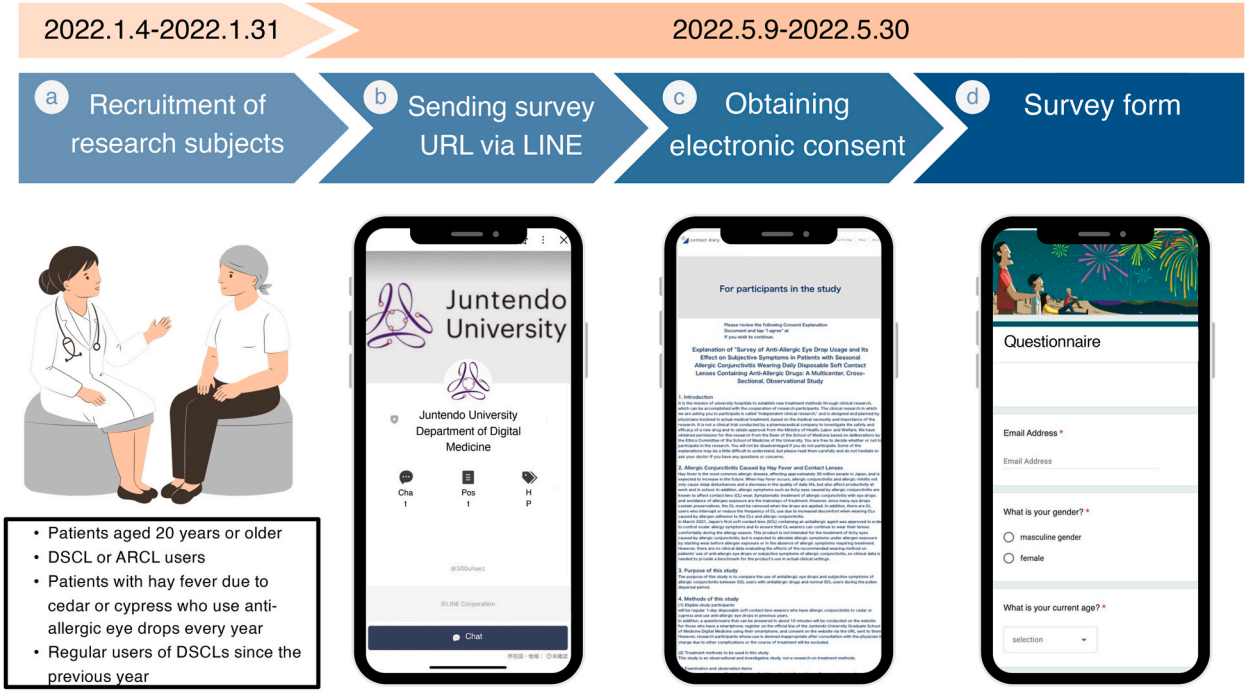

Fig. 1. Diagram showing the study procedure (a) Participant inclusion criteria (b) Screenshot of the official LINE account of the study's host department. (c) Screenshot of the electronic patient consent form on the linked web page (d) Screenshot of the questionnaire on the web created using Google Forms. ARCL: antihistamine-releasing contact lens, CL: contact lens, DSCL: daily disposable soft contact lens, URL: uniform resource locator.

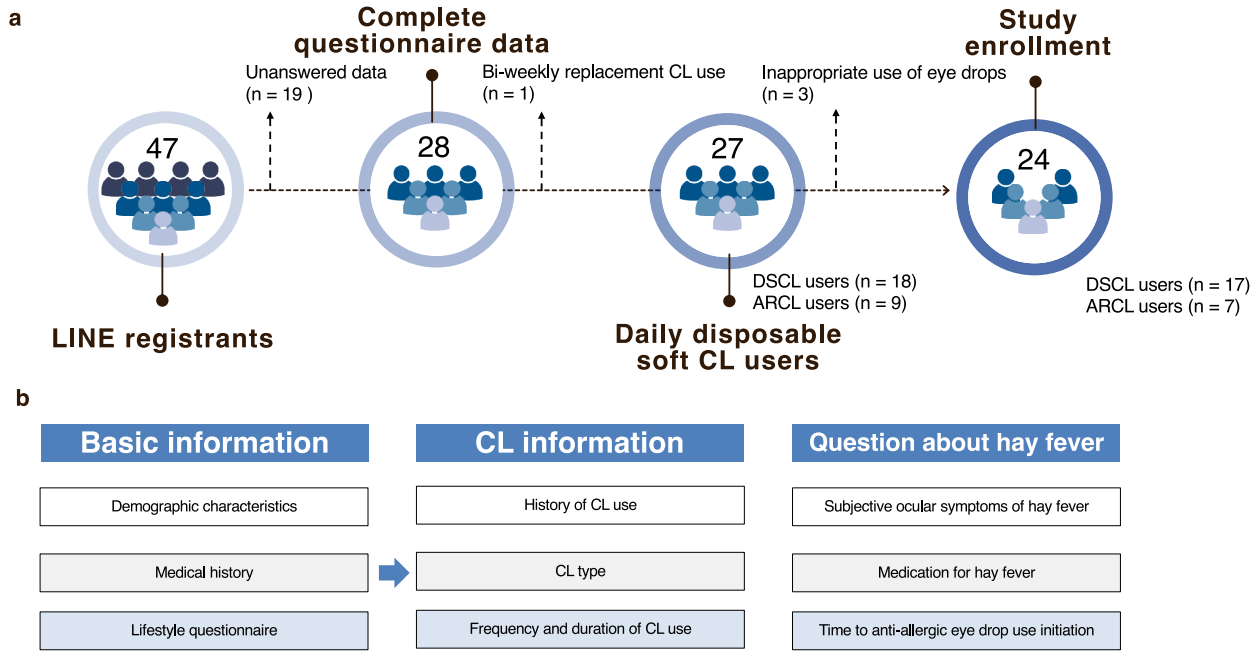

Fig. 2. Study cohort description (a) Flow diagram showing the participants' enrollment. (b) Flowchart of items in the web survey form. CL; contact lens, DSCL; daily disposable soft contact lens, ARCL; antihistamine-releasing contact lens.

2.5. ARCL

The ARCLs (Acuvue Theravision with Ketotifen, Johnson & Johnson Vision Care, MA, US) used are etafilcon-based DSCLs that are the world's first CLs containing ketotifen (anti-allergic drug) [6,17].

2.6. Statistical analysis

To compare the characteristics of the study participants between the DSCL and ARCL groups, an unpaired *t*-test was used for continuous variables and an χ^2 test was used for the categorical variables. Kaplan–Meier analysis was performed to construct the curves from the beginning of hay fever season (February 1, 2022) to anti-allergic eye drop use initiation. The survival curves were compared between the two groups using a log-rank test. Participants who were not using the anti-allergic eye drops were censored at the time of the survey. Statistical analyses were performed using GraphPad Prism (version 10.0.2, La Jolla, CA, USA). Statistical significance was set at $P < 0.05$.

The required sample size was based on the assumption of using a log-rank test to compare the number of days from the start of pollen dispersal to the start of anti-allergy eye drop administration between the DSCL and ARCL users. When the hazard ratio was set at 0.2, the sample size ratio of the DSCL users to the ARCL users was 2:1, the significance level was 5 %, and the power was 95 %, the required sample size was calculated to be 16 and 7 for the DSCL and ARCL users, respectively [18]. Considering a dropout rate of 20 %, the target sample size was set at 20 in the DSCL users and 9 in the ARCL users, for a total of 29 users.

3. Results

3.1. Study enrollment

Fig. 2a illustrates the study enrollment procedure. Participant recruitment was conducted between January 4 and January 31, 2022 in Japan. Subsequently, after the peak pollen dispersal in Japan [2], survey uniform resource locators were distributed with registered patients between May 9 to May 31, 2022, with 47 individuals registered on LINE (LINE Corporation, Tokyo, Japan). Among them, 19 individuals were excluded due to incomplete data; thus, 59.6 % (28 of 47) individuals completed the survey, and four individuals were excluded due to bi-weekly replacement CL use (n = 1) and anti-allergic eye drop use before the hay fever season (n = 3). Finally, a total of 24 participants were enrolled following the completion of the entire questionnaire. Participant (included and excluded) characteristics are presented in Supplementary Table 2.

3.2. Participant characteristics

Of the 24 participants, 17 (70.8 %) used DSCLs and 7 (29.2 %) used ARCLs. Participant characteristics are presented in Table 1. The mean age ± standard deviation (SD) of all included participants was 32.8 ± 11.6 years, and 83.3 % of the participants were female. Among them, 62.5 % reported a history of taking oral anti-allergy medication during the pollen dispersal period. No statistically significant differences between the two groups were observed in demographic characteristics, lifestyle, medical history, and history of CL use.

3.3. Subjective ocular symptoms during hay fever seasons

Table 2 presents the subjective ocular symptoms during the hay fever season in 2021 and 2022 and reveals no significant differences between the groups. Fig. 3a shows the changes in TOSS between the DSCL users and ARCL users. In total, 85.7 % (6/7) of ARCL users exhibited an improvement in the TOSS and no participants (0 %, 0/7) exhibited a worsening of the TOSS in 2022 compared with the scores in 2021. In contrast, 52.9 % (8/17) of DSCL users exhibited a worsening of the TOSS or constant TOSS. Fig. 3b shows the comparison of the change in TOSS between DSCL users and ARCL users. The TOSS reduced considerably more from 2021 to 2022 in ARCL users than in DSCL users (mean change in TOSS [SD]: DSCL users: −0.65 [1.4], ARCL users: −4.7 [3.6]; Mann–Whitney *U* test, n = 24, $P = 0.010$).

3.4. Time to anti-allergic eye drop use initiation during the hay fever season

Fourteen (82.4 %) DSCL users and five (71.4 %) ARCL users required the administration of anti-allergic eye drops during the study period. Kaplan–Meier analysis (Fig. 4a) revealed that the time from the beginning of the hay fever season to anti-allergy eye drop use initiation was longer in ARCL users than in DSCL users (Fig. 4b; median days; DSCL users: 19 days, ARCL users: 57 days; n = 24; log-rank test, $P = 0.045$).

4. Discussion

SAC due to underlying hay fever frequently causes ocular irritation, foreign body sensation, and excessive watery discharge, leading to CL discontinuation even in long-term CL users. Here, we conducted a web-based retrospective cohort study comparing various ocular symptoms and ocular treatment behaviors between regular DSCL users and users of the world's first ARCL. Participants with known hay fever and SAC using ARCLs expressed significantly improved TOSS than that in the previous year and a delay in starting anti-allergic eye drops compared with those using DSCLs. Our results indicate that proactively wearing ARCLs before hay fever and SAC onset may effectively prevent and suppress the SAC onset and aggravation.

CLs are widely accepted as an effective and convenient option for correcting refractive errors; the estimated number of CL users is approximately 125 million [19]. However, the direct effects of placing CLs on the highly sensitive ocular surface cause a wide range of

Table 1
Characteristics of the study participants.

Characteristics	DSCL users	ARCL users	*P* value	Total
	n = 17	n = 7		n = 24
Demographic characteristics				
Age, years ±SD	34.2 ± 12.0	29.7 ± 10.7	0.394	32.8 ± 11.6
Sex, female (%)	14 (70.8)	6 (85.7)	0.841	20 (83.3)
Lifestyle				
Exercise, hours per day, h ± SD	1.0 ± 1.8	0.9 ± 0.7	0.842	1.0 ± 1.5
Having a pet (%)	6 (35.3)	0 (0)	0.070	6 (25.0)
Sleep, hours per day, h ± SD	6.3 ± 1.0	6.6 ± 1.7	0.621	6.4 ± 1.2
Smoking (%)	2 (11.8)	1 (14.3)	0.841	3 (12.5)
Time spent in outdoor activities during the hay fever season, hours per day, h ± SD	1.9 ± 1.6	2.7 ± 4.2	0.702	2.1 ± 2.5
Medical history				
Atopic dermatitis (%)	1 (5.9)	0 (0)	0.512	1 (4.2)
Cataract (%)	1 (5.9)	0 (0)	0.512	1 (4.2)
Dry eye disease (%)	1 (5.9)	0 (0)	0.512	1 (4.2)
Glaucoma (%)	0 (0)	1 (14.3)	0.111	1 (4.2)
Keratoconus (%)	1 (5.9)	0 (0)	0.512	1 (4.2)
Retinal disease (%)	1 (5.9)	2 (28.6)	0.156	3 (12.5)
History of CL use				
Years of CL use, y ± SD	15.5 ± 10.4	13.9 ± 10.7	0.725	15.0 ± 10.3
Days of CL use per week during the hay fever season, d ± SD	6.2 ± 1.4	6.4 ± 0.8	0.873	6.3 ± 1.2
Hours of CL use per day during the hay fever season, h ± SD	12.4 ± 2.7	11.6 ± 3.1	0.584	12.1 ± 2.8
History of oral anti-allergic medication use (%), yes	64.7 %	57.1 %	>0.99	62.5 %

P values were determined using the Student's *t*-test (two-tailed) for continuous variables and the χ^2 test for categorical variables. ARCL; antihistamine-releasing contact lens, CL; contact lens, CLD; contact lens discomfort, DSCL; daily disposable soft contact lens, SD; standard deviation.

Table 2
Ocular symptoms during the hay fever season.

Ocular symptoms	DSCL users	ARCL users	*P*-value	Total
	n = 17	n = 7		n = 24
Ocular symptoms in 2021, 0–4 (SD)				
Itchy eyes	1.7 (0.8)	2.3 (1.6)	0.424	1.9 (1.1)
Foreign body sensation	1.2 (1.0)	1.7 (1.5)	0.466	1.4 (1.1)
Red eyes	0.7 (0.8)	1.7 (1.6)	0.146	1.0 (1.2)
Watery eyes	0.9 (0.9)	1.3 (1.4)	0.634	1.0 (1.0)
Eye discharge	0.8 (0.8)	1.6 (1.6)	0.311	1.0 (1.1)
Total ocular symptoms in 2021, 0–20 (SD)	5.3 (3.5)	8.6 (6.7)	0.403	6.3 (4.8)
Ocular symptoms in 2022, 0–4 (SD)				
Itchy eyes	1.6 (0.8)	1.3 (1.0)	0.368	1.5 (0.8)
Foreign body sensation	1.0 (1.0)	0.9 (0.7)	0.922	1.0 (0.9)
Red eyes	0.5 (0.7)	0.4 (0.8)	0.718	0.5 (0.7)
Watery eyes	0.8 (0.8)	0.4 (0.8)	0.314	0.7 (0.8)
Eye discharge	0.8 (0.9)	0.9 (0.9)	0.967	0.8 (0.9)
Total ocular symptoms in 2022, 0–20 (SD)	4.7 (3.0)	3.9 (3.8)	0.260	4.5 (3.2)

P values were determined using the Mann–Whitney *U* test (two-tailed) for continuous variables. ARCL; antihistamine-releasing contact lens, DSCL; daily disposable soft contact lens.

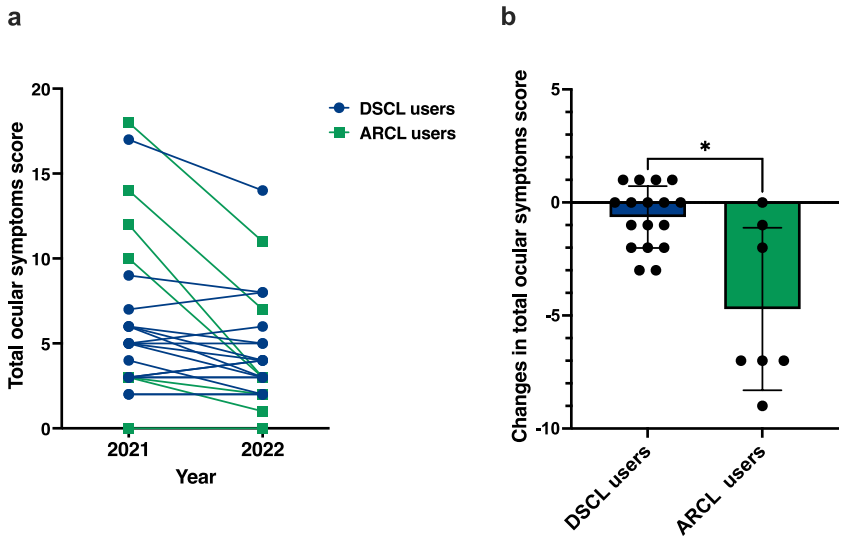

Fig. 3. Ocular symptoms during the hay fever season compared between DSCL and ARCL users (a) Individual changes in total ocular symptom score between DSCL users and ARCL users. (b) Comparison of the changes in total ocular symptom score between DSCL users and ARCL users. ARCL; antihistamine-releasing contact lens; DSCL; daily disposable soft contact lens.

symptoms, such as ocular discomfort, and, in severe cases, lead to pathologies such as CLPC, ultimately discouraging CL use, even among long-term users [6,7]. Previous literature suggests that more than 20 % of CL users experience an SAC exacerbation due to long-term CL use [20]. The current standard of care for allergic conjunctivitis revolves around symptomatic treatment using topical antihistamines and steroids; however, due to concerns of infection and the effects of preservatives contained in topical drops, CLs are recommended to be discontinued during active treatment [9,21,22]. Therefore, closely monitoring long-term CL users' hay fever symptoms and adherence to topical regimens may be fundamental in preventing and suppressing SAC during high pollen seasons. While the field awaits widespread clinical application, notable recent efforts to develop novel SAC management tools include smartphone app-based recognition of digital phenotypes [2,23,24] and longitudinal evaluation of hay fever symptoms with simultaneous monitoring of topical treatment adherence [15,16,25].

This study observed a significantly greater year-to-year decrease in SAC ocular subjective symptoms during the hay fever season in ARCL users than in DSCL users. Previous studies reported that ARCL users showed comparable results with six patients with well-controlled allergic conjunctivitis [9,11]. Moreover, drug-releasing CLs appear to have two major advantages over direct topical application of medications to the ocular surface. First, benzalkonium chloride, a now-ubiquitous antimicrobial preservative for ophthalmic preparations, exerts cytotoxic damage to conjunctival and corneal cells, exacerbating existing CLPC [8]. However, CL-based drug delivery utilizes a well-protected aqueous layer between the lens and the cornea where the released medication can remain on the ocular surface without being subjected to rapid tear drainage [26]. In summary, ARCL users may benefit from avoiding

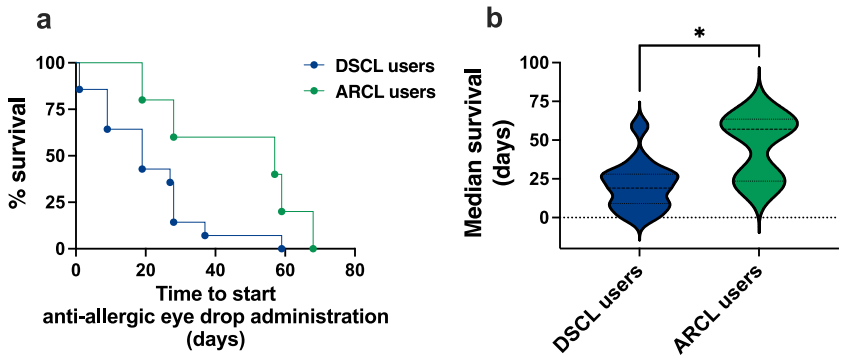

Fig. 4. Time to anti-allergic eye drop use initiation during the hay fever season (a) Kaplan–Meier curves showing that ARCL users exhibited a significant delay in initiating the use of anti-allergic eye drops during the hay fever season compared with DSCL users. (b) Median time to anti-allergic eye drop use initiation from February 1st, 2022, the beginning of hay fever season in Japan (in days; DSCL users: 19 days; ARCL users: 57 days; n = 24, log rank test, $P = 0.045$). ARCL; antihistamine-releasing contact lens, DSCL; daily disposable soft contact lens.

ocular surface exposure to benzalkonium chloride cytotoxicity altogether, while steadily receiving the released ketotifen with minimal concern for drug washout.

In addition to decreased subjective symptoms, our results indicate that ARCL users spent a longer period before requiring topical anti-allergic eye drops from the start of the hay fever season for symptom management compared with DSCL users. Thus, patients with SAC due to hay fever may benefit from proactive, preventive interventions before developing ocular symptoms, such as initiating pre-seasonal treatment, which helps suppress the onset or prevents exacerbation [27,28]. Our observation likely reflects the role of alleviating and preventing ocular symptoms using ARCLs, leading to delayed initiation of topical treatment. As previously noted, it is important to recognize that proactive treatment is crucial in managing allergic conjunctivitis by administrating anti-allergic eye drops at an appropriate rate (strict frequency and timing) and, consequently, adhering to the prescribed regimen [28]. Thus, ARCLs, particularly in daily CL users, should decrease the concern of unpredictable adherence and enable proactive treatment before hay fever seasons through the built-in drug delivery system. Therefore, recommending a transition to ARCLs for patients with hay fever before SAC onset during high pollen season may potentially reduce allergic responses and decrease the incidence rate and severity of CLPC in a large population of CL users.

Nonetheless, this study had some limitations. First, the results were subject to recall bias due to the use of a questionnaire to collect ocular symptoms experienced in the past. The questionnaires were distributed in May 2022, following the hay fever season. The potential for recall bias may not be negligible as the participants were asked to recall details of their symptoms that occurred at least several months before receiving the questionnaire. Additionally, this study assessed symptomatic SAC solely based on web-based surveys; consequently, we were unable to accurately characterize the clinical phenotypes and initial presentations of SAC in the participants. Second, as this study was a retrospective cohort study with limited numbers of participants in the ARCLs group and not a randomized trial, the ARCL and DSCL cohorts were not systematically assigned to address any confounding variables, including lifestyles, materials and types of contact lens, and type of allergens of hay fever; hence, one's predisposition to allergic conjunctivitis and disease severity may have affected the selection of CL material and type, exposing the results to a degree of selection bias. However, as the study participants were carefully selected based on known prior history of cedar and cypress pollen hay fever, along with the study period focused on high cedar and cypress pollen dispersion seasons, we believe that the selection bias related to allergen types is minimal. Moreover, those who experienced allergic conjunctivitis due to hay fever or CLPC in the past and those with prior knowledge of or interest in ARCLs are thought to be more likely to transition to ARCLs than typical CL users. However, both cohorts did not show significant differences in patient characteristics in this study (Table 1). Therefore, future studies should implement randomization of study groups to address the biases mentioned above and control confounding variables to confirm the anti-allergic effects of ARCLs for patients with hay fever-related allergic conjunctivitis. Despite these limitations, our study results may be one of the earliest pieces of evidence supporting the utility of ARCLs in suppressing allergic conjunctivitis using a web-based retrospective cohort study on a CL-based drug delivery system.

5. Conclusions

In conclusion, the results of this study suggest that ARCLs are effective in reducing ocular symptoms and delaying the initiation of topical anti-allergic medications during hay fever seasons in patients with SAC. By recommending the proactive use of ARCLs before symptom onset or in high pollen months, patients with hay fever who are long-term CL users should experience improved suppression of SAC and CLPC. Furthermore, these findings may have implications in establishing new preventive strategies using a CL-based drug delivery system in preparation for annual high pollen seasons for CL users among patients with hay fever.

Ethical statement

This study was approved by the Independent Ethics Committee of Juntendo University Faculty of Medicine (approval number: E21-0220-H01). This study adhered to the tenets of the Declaration of Helsinki. Electronic informed consent was obtained from all participants.

Data availability statement

The data that support the findings of this study are available upon request from the corresponding author [T.I.]. The data are not publicly available as the containing information could compromise the privacy of research participants.

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CRediT authorship contribution statement

Kenta Fujio: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Jaemyoung Sung:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Kunihiko Hirosawa:** Writing – review & editing, Writing – original draft, Data curation. **Masahiro Yamaguchi:** Writing – review & editing, Writing – original draft, Validation. **Hiroshi Toshida:** Writing – review & editing, Writing – original draft, Validation. **Keiji Inagaki:** Writing – review & editing, Writing – original draft, Validation. **Gaku Ishida:** Writing – review & editing, Writing – original draft, Validation. **Motozumi Itoi:** Writing – review & editing, Writing – original draft, Validation. **Kazushige Sado:** Writing – review & editing, Writing – original draft, Validation. **Hiroo Hayatsu:** Writing – review & editing, Writing – original draft, Validation. **Hirayama Nobutaka:** Writing – review & editing, Writing – original draft, Validation. **Junji Ono:** Writing – review & editing, Writing – original draft, Validation. **Hidetaka Taniguchi:** Writing – review & editing, Writing – original draft, Validation. **Masao Iwagami:** Writing – review & editing, Writing – original draft, Validation. **Ken Nagino:** Writing – review & editing, Writing – original draft, Validation. **Yuichi Okumura:** Writing – review & editing, Writing – original draft, Validation. **Akie Midorikawa-Inomata:** Writing – review & editing, Writing – original draft, Methodology. **Yasutsugu Akasaki:** Writing – review & editing, Writing – original draft, Validation. **Tianxiang Huang:** Writing – review & editing, Writing – original draft, Validation. **Yuki Morooka:** Writing – review & editing, Writing – original draft, Validation. **Tomoko Okuyama:** Writing – review & editing, Writing – original draft, Validation. **Shintaro Nakao:** Writing – review & editing, Writing – original draft, Validation. **Akira Murakami:** Writing – review & editing, Writing – original draft, Validation. **Hiroyuki Kobayashi:** Writing – review & editing, Writing – original draft, Validation. **Takenori Inomata:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Takenori Inomata reports equipment, drugs, or supplies was provided by Lion Corporation. Takenori Inomata reports equipment, drugs, or supplies was provided by Sony Network Communications Inc. Takenori Inomata reports financial support was provided by Kandenko, Co., Ltd., Johnson & Johnson K.K. Vision Care Company, Yuimedi, Inc., Rohto Pharmaceutical Co., Ltd., Kobayashi Pharmaceutical Co., Ltd., and Fukoku Co., Ltd. Takenori Inomata reports financial support was provided by Santen Pharmaceutical Co., Ltd., InnoJin, Inc., and Ono Pharmaceutical Co., Ltd. Takenori Inomata reports a relationship with InnoJin, Inc that includes: equity or stocks. Shintaro Nakao reports financial support was provided by Kowa Company Ltd., Mitsubishi Tanabe Pharma Corporation, Alcon Japan, Ltd., Santen Pharmaceutical Co., Ltd., Machida Endoscope Co., Ltd., Wakamoto Pharmaceutical Co., Ltd., Bayer Yakuhin, Ltd., Senju Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Chugai Pharmaceutical Co., Ltd., Hoya Corporation, and Novartis Pharma K.K., outside the submitted work. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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