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ORIGINAL RESEARCH

Efficacy of Proactive Topical Antihistamine Use in Patients with Seasonal Allergic Conjunctivitis

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ABSTRACT

Introduction: Topical antihistamines are often instilled symptomatically to control patients' eye allergy symptoms. The purpose of this study was to evaluate the effectiveness of proactive and as-needed use of antihistamine eye drops in controlling symptoms and to examine whether proactive use may improve quality of life (QOL).
Methods: This was a prospective, multicenter, cohort study in Japan. We classified 418 patients who had developed certain symptoms and used antihistamine eye drops for 2 weeks into two groups: those who used the drops at the required frequency at a fixed time (proactive use) and those who used them as-needed. The Japanese Allergic and Conjunctival Diseases Quality of Life Questionnaire (JACQLQ) and Ten-Item Personality Inventory were used to evaluate QOL and personality. Participants' QOL was evaluated using JACQLQ scores after matching of baseline characteristics using propensity score analysis.
Results: After propensity score matching, 115 "proactive" and 115 "as-needed" patients were analyzed. After treatment, in "as-needed" patients, the overall QOL scale was 1.66 (95% CI 1.55–1.78); in "proactive" patients, the overall QOL scale was 1.34 (95% CI 1.23–1.46) and was significantly improved compared with the "as-needed" patients (analysis of covariance, $P = 0.002$). Furthermore, proactive use significantly alleviated depression ($P = 0.03$). This improvement of QOL was independent of improvement of the clinical sign scores.
Conclusion: Proactive use of topical antihistamine may serve as an effective means for

Atsuki Fukushima and Dai Miyazaki contributed equally to this study.

The Proactive Study Group members are listed in the Acknowledgments.

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improving QOL of patients with seasonal allergic conjunctivitis.
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Key Summary Points

Why carry out this study?

Most patients with allergic conjunctivitis, seeking quick relief, might use antihistamine eye drops for symptom alleviation. However, this method of using eye drops does not provide sufficient therapeutic effect and cannot improve QOL.

The hypothesis of this study was that proactive use was advantageous in improving QOL of patients with SAC throughout the pollen season.

What was learned from the study?

Proactive use of antihistamine eye drops is an effective means for improving the QOL and mental status of patients with SAC during the pollen season.

If the concentration of antihistamines can be maintained throughout the pollen season by proactive use of antihistamine eye drops, this method is expected to block H_1 receptors in advance and reduce the occurrence of itching.

INTRODUCTION

Antihistamine eye drops constitute first-line treatment for allergic conjunctival diseases and have been reported to effectively reduce clinical symptoms and improve quality of life (QOL) in patients with seasonal allergic conjunctivitis (SAC) [1]. Most patients with allergic conjunctivitis, seeking quick relief, might use the antihistamine eye drops for symptom alleviation [2].

To maintain QOL, a method of continuously suppressing allergic symptoms and inflammation in advance may be considered. For example, if the concentration of antihistamines can be maintained throughout the pollen season, it might be possible to maintain QOL.

The efficacy of using antihistamines at the required frequency and at a fixed time (hereinafter referred to as proactive use) in patients who have already developed certain symptoms has been investigated in otolaryngology. Ciprandi et al. examined the effect of oral administration either continuously or on demand [3]. The results showed that patients treated with continuous administration of cetirizine achieved significant symptomatic relief and inflammatory control compared with the patients treated on demand. In the field of ophthalmology, studies have evaluated the difference between regular use and as-needed use of mast cell stabilizers [4], but to date no studies have reported on the use of antihistamine eye drops. In studies using mast cell stabilizers, eye drops were started before the onset of symptoms, but to date no studies have evaluated the difference in eye drop method after the onset of symptoms.

Many factors can be considered in relation to the adherence of patients with SAC to an instillation regimen. This study also focused on personality as the factor that most influences instillation behavior among many factors that affect it. The personality inventory consists of five main components: neuroticism, extraversion, agreeability, conscientiousness, and openness [5]. For example, in individuals with asthma, neuroticism has been associated with lower adherence [6–8], whereas conscientiousness has been associated with higher adherence to asthma medication treatment [6]. Additionally, medication routines for asthma treatment were associated with neuroticism and conscientiousness [7].

We, therefore, conducted a large prospective cohort study to evaluate QOL as a measure of the efficacy of proactive and as-needed antihistamine eye drop use in patients who had

already developed symptoms, and shall show proactive use is advantageous in improving QOL of patients with SAC throughout the pollen season.

METHODS

Compliance with Ethics Guidelines

This study was performed following the principles of the Declaration of Helsinki and with the Ethical Guidelines for Medical and Health Research Involving Human Subjects. All patients were given a full explanation of the study and all provided written informed consent to participate. This study was approved by the Institutional Review Board of the TOUKEI-KAI Kitamachi Clinic and was registered with UMIN-CTR (http://www.umin.ac.jp/, Identification No. UMIN000039554).

Study Design

This study was a prospective, multicenter, cohort study at 16 sites in Japan. At the time of informed consent (0 weeks), the following data were collected: patient background, the personality inventory, and the Japanese Allergic and Conjunctival Diseases QOL Questionnaire (JACQLQ) [9]. Patients then began antihistamine eye drops use for 2 weeks. We mailed the questionnaire 2 weeks after the visit and asked the patients to return them to the site after completion. At 2 weeks, the following data were collected: how they used antihistamine eye drops and the completed JACQLQ. Regarding the questionnaire after 2 weeks, a questionnaire completed 2–5 weeks after obtaining the consent was judged to be a valid response.

Participants

This study recruited patients who visited the site to begin treatment for SAC between February and March 2020. The patients provided written informed consent and met all the inclusion criteria and none of the exclusion criteria. The inclusion criteria were as follows: (1) 20 years of age or older; (2) diagnosed with SAC before 2019 at the site of the study; (3) with a subjective symptom such as itchy eyes at week 0, and with an eye itching score of 2 or higher on the JACQLQ; and (4) began antihistamine eye drop use at week 0.

The exclusion criteria were as follows: (1) severe allergic conjunctival disease (vernal keratoconjunctivitis or atopic keratoconjunctivitis); (2) pre-seasonal treatment for SAC after the end of 2019; and (3) beginning antihistamine eye drop use before week 0. The inclusion and exclusion criteria were intended to minimize the effect on endpoints and to improve the reliability of the survey results.

We determined the sample size required for the study as a whole by referring to the study by Fukagawa et al. [10]. The normal administration group in the previous study ($N = 90$) was assumed to be the as-needed use group. We set 2.6 ± 8.2 as the difference between the change in the proactive eye drop group and the symptomatic eye drop group for the change in the total JACQLQ II-QOL score. We set the number of cases per group at 2.6 ± 8.2 and calculated 81 cases per group as the required number to be detected at a significance level of 5% and a power of 80%.

Patient Background

We collected the following information from medical records and patients: age, gender, use of contact lens in daily life, type of antihistamine eye drops, presence of other allergic diseases, and treatment for allergic diseases (including over-the-counter drugs).

The Personality Inventory

The association between medication compliance and personality has already been examined in another allergic disease, asthma [6–8]. To adjust for confounding factors including personality, the personality inventory was

assessed with the Ten-Item Personality Inventory (TIPI-J) [5]. The TIPI-J evaluates the Big Five personality traits. In previous studies, adherence had been correlated with conscientiousness and neuroticism [6–8]. Therefore, taking into account the burden on the patient, we collected the following TIPI-J questions that were assumed to affect the association between proactive use and as-needed use: Q3, dependable, self-disciplined; Q4, anxious, easily upset; Q8, disorganized, careless; and Q9, calm, emotionally stable. The TIPI-J questions are scored from 1 (strongly disagree) to 7 (strongly agree). To evaluate each personality trait, the scores were calculated as follows [11]: conscientiousness: [Q3 + (8 − Q8)]/2; and neuroticism: [Q4 + (8 − Q9)]/2.

Questionnaire

The primary outcomes were symptoms and QOL as evaluated by the JACQLQ version 1 [9]. Patients completed the JACQLQ at the time of informed consent (week 0) and at week 2. The JACQLQ contains 27 questions divided into three subscales: eye and nasal symptoms, QOL, and overall QOL scale (Table 1). The overall QOL scale was a facial imaging scale based on the patient's general state. Additionally, the mean scores (± SD) at each time point and the amount of change in scores from week 0 to week 2 were calculated.

The total subjective symptoms and six areas in QOL are as follows. Eye symptoms: symptom 01 (itchy eyes) to symptom 05 (eye grease). Eye and nasal symptoms: symptom 01 (itchy eyes) to symptom 09 (itchy nose). Usual daily activities: QOL01 (reduced productivity at work/home) to QOL05 (decreased memory loss). Outdoor activities: QOL06 (limitation of outdoor life), QOL07 (limitation of going out). Social functioning: QOL08 (hesitation visiting friends or relatives) to QOL10 (not an easy person to be around). Impaired sleep: QOL11 (impaired sleep). Physical problems: QOL12 (tiredness) and QOL13 (fatigue). Emotional function: QOL14 (frustration) to QOL17 (unhappiness).

Table 1 Japanese Allergic and Conjunctival Diseases Quality of Life Questionnaire

Category	
I. Eye and nasal symptoms	
Symptom 01	Itchy eyes
Symptom 02	Foreign body sensation
Symptom 03	Hyperemia
Symptom 04	Watery eyes
Symptom 05	Eye discharge
Symptom 06	Runny nose
Symptom 07	Sneezing
Symptom 08	Nasal congestion
Symptom 09	Itchy nose
II. Quality of life	
QOL 01	Reduced productivity at work/home
QOL 02	Poor mental concentration
QOL 03	Reduced thinking power
QOL 04	Impaired reading of book/newspaper
QOL 05	Reduced memory loss
QOL 06	Limitation of outdoor life
QOL 07	Limitation of going out
QOL 08	Hesitation visiting friend or relatives
QOL 09	Reduced contact with friends or others by telephone or conversation
QOL 10	Not an easy person to be around
QOL 11	Impaired sleep
QOL 12	Tiredness
QOL 13	Fatigue

Table 1 continued

Category	
QOL 14	Frustration
QOL 15	Irritability
QOL 16	Depression
QOL 17	Unhappiness
III. Overall QOL scale (facial imaging scale)	

Comparison of the Proactive Use Group with the As-needed Use Group

To understand how patients used antihistamine eye drops for 2 weeks after the start of eye drop use, the following three questions were asked at 2 weeks: Question 1 asked, "Did you practice proactive use or as-needed use in terms of the antihistamine eye drops?" The possible answer options were "proactive use," defined as regular use regardless of symptoms such as eye itching; and "as-needed use," defined as using eye drops only when the patient felt symptoms such as eye itching. Question 2 asked the number of times antihistamine eye drops were used per day. Question 3 asked the participants whether they had taken antihistamine eye drops on time as instructed by their doctor.

After collecting the questionnaires, the patients were classified into a proactive use group and an as-needed use group. The proactive use group was defined as patients who used an antihistamine eye drop as instructed at the approved dose based on drug kinetics and used it regularly regardless of symptoms such as eye itching. Those who selected all of the following items for Questions 1 through 3 were considered to be eligible for the study: For Question 1, the patient selected "proactive use"; for Question 2, the patient selected the approved dosage for each eye drop, and for Question 3, the patient used eye drops as instructed by their doctor. The as-needed use group was defined as patients who used antihistamine eye drops only when they felt symptoms such as eye itching. Those who selected "use as needed" in Question 1 were considered to be in this group. The instructed dose for each eye drop was as follows: epinastine hydrochloride 0.1%, twice daily (morning and evening); eye drops except epinastine hydrochloride 0.1%, four times daily (morning, afternoon, evening, and before bedtime).

Propensity Score Matching

The association between proactive use and as-needed use was possibly affected by many factors, such as the personality and symptom level of the patients. Therefore, we selected 19 categories based on the patient background as the candidate covariates. The candidate covariates were as follows: age, gender, contact lens wearing, type of antihistamine eye drops, presence of other allergic diseases (allergic rhinitis, asthma, and atopic dermatitis), and treatment for allergic diseases (steroid eye drops, antiallergic eye drops, oral drugs, and nasal drugs), and the eye symptom score at week 0 (itchy eyes, foreign body sensation, hyperemia, watery eyes, and eye discharge). We selected the covariates on the basis of the univariate analysis results and logistic model analysis results, using a stepwise method that could be associated with the outcome of interest and treatment groups. We calculated the propensity score of the treatment groups by fitting a logistic regression model, using covariates. We measured the imbalance between covariates employing standardized differences of the mean for both the continuous and categorical variables, whereby an absolute standardized difference above 10% represents meaningful imbalance. We used the nearest-neighbor method, with a 1:1 ratio for the proactive use group vs. the as-needed use group.

Overall QOL Scale and Each JACQLQ Question by Principal Component Analysis

Principal component analysis was conducted to examine the relationship between the overall QOL scale and each JACQLQ question. The contribution ratio of the principal component

(PC) 1 was 41.0%. All the JACQLQ questions correlated with PC1 (Supplementary Fig. S1).

We performed a multiple regression analysis using the score of the factor component with an eigenvalue of 1 or greater as the independent variable and the change in the score of the overall QOL scale over 2 weeks as the dependent variable. As the result, PC1 was the overall QOL scale and a significant variable ($P < 0.001$). Based on the results of the principal component analysis and multiple regression analysis, the overall QOL scale was considered to be the aggregate of all questions except the overall QOL scale in JACQLQ.

Statistical Analysis

We used SAS Version 9.4 (SAS Institute, Cary, NC, USA) and IBM SPSS Statistics 25.0 (IBM Corp, Armonk, NY, USA). We performed the Aspin–Welch *t* test on the continuous data and the Fisher's exact test on the categorical data for the basic statistic. The significance level of the two-sided test was set at 5%.

In the comparison of JACQLQ scores between the proactive use and as-needed use groups, we used the *t* test for the population before and after propensity score matching. To adjust baseline covariates, analysis of covariance (ANCOVA) was used. Each question for the JACQLQ scores was summarized using principal component analysis, and standardized partial regression scores were calculated.

RESULTS

Characteristics of the Study Patients Before Propensity Score Matching

In total, 418 patients were enrolled, and 403 patients responded to the questionnaire after 2 weeks. Ultimately, 325 patients were analyzed in this study. Before propensity score matching, there were 160 patients classified into the proactive use group, and 165 patients classified into the as-needed use group (Fig. 1).

Table 2 shows the background characteristics of the patients before and after propensity score matching. For the 19 categories that were candidates for covariates in the propensity score matching, the patients in the proactive use group before propensity score matching were older in age ($P = 0.011$); had a higher rate of women ($P = 0.003$); and had a different distribution of prescribed antihistamine eye drops ($P < 0.001$) than the as-needed use group. Regarding treatment of allergic diseases other than antihistamine eye drops, no significant bias was found between the two treatment groups, such as steroid eye drops. Also, Supplementary Table S2 shows the pre- and post-treatment JACQLQ scores between the two treatment groups before propensity score matching.

Comparison of the Proactive Use Group with the As-needed Use Group After Propensity Score Matching

After propensity score matching (the proactive use group/the as-needed use group, 1:1) by adjusting the covariates, including age, gender, the "disorganized, careless" personality inventory, type of antihistamine eye drops, use of steroid eye drops, and the itchy eyes score, each treatment group matched 115 patients. After propensity score matching, all the covariates between the groups were matched (Supplementary Table S1).

Regarding the JACQLQ symptom scores between the two treatment groups, the mean scores of eye symptoms (other than itchy eyes) were already mild on the baseline score, ranging from 1.0 to 1.4 (1.0 = mild). In contrast, both groups showed improvement from baseline in their scores at 2 weeks, but no significant between-group differences were observed for the following symptoms: itchy eyes ($P = 0.25$), foreign body sensation ($P = 0.41$), hyperemia ($P = 0.23$), watery eyes ($P = 1.00$), eye discharge ($P = 0.71$), as shown in Supplementary Table S3.

Comparing the changes in QOL scores on the JACQLQ, the improvement of the overall QOL scale score in the proactive use group after propensity score matching was significantly greater than in the as-needed use group ($P = 0.02$). The scores in the six areas in the

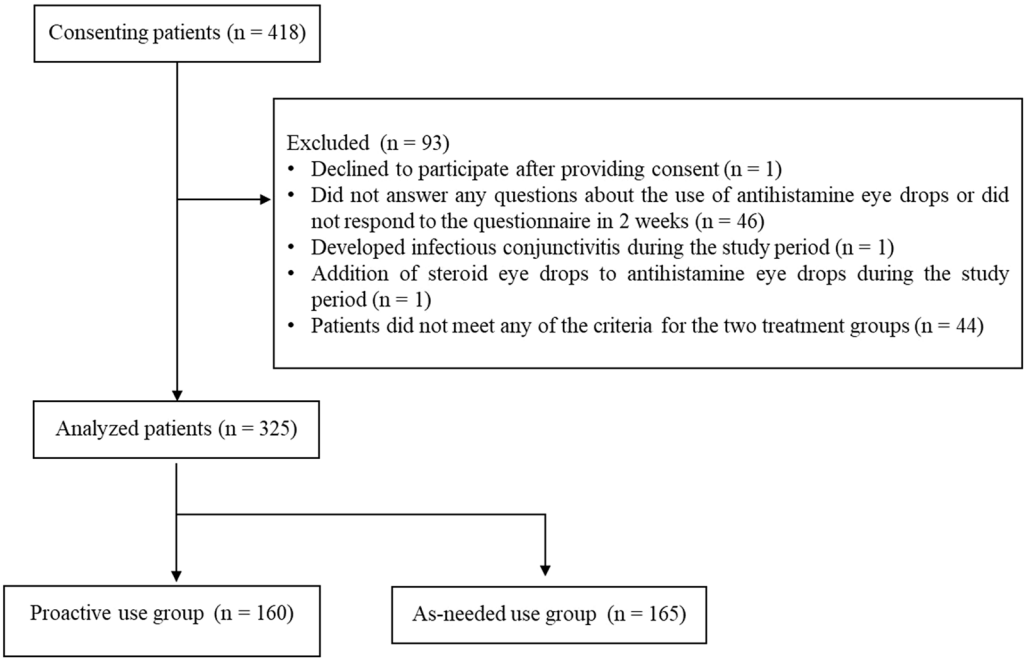

Fig. 1 Diagram of enrollment and exclusion of patients. The data represent the flow of patients in the study. Consent was obtained for 418 patients; 325 were included in the analysis, excluding patients who did not completely describe in the questionnaire after 2 weeks, and patients who did not fall into the two treatment groups

QOL-related questionnaires improved in both groups; nevertheless, no significant difference between the two treatment groups was found (Supplementary Table S3).

Because the baseline score was assumed to affect the amount of change in the JACQLQ score, we conducted an ANCOVA with the baseline score as an adjustment factor. The ANCOVA with baseline as an adjustment factor showed that the estimates (95% confidence interval; CI) of the overall QOL scale in the proactive use group improved from 2.11 (95% CI 2.00–2.23) to 1.34 (95% CI 1.23–1.46, Table 3). The estimates (95% CI) of the overall QOL scale in the as-needed use group improved from 2.14 (95% CI 2.02–2.25) to 1.66 (95% CI 1.55–1.78); and the improvement of the overall QOL scale score in the proactive use group after propensity score matching was significantly greater than that in the as-needed use group ($P = 0.002$).

Furthermore, in the area of emotional functions, the estimates (95% CI) of "depression" in the proactive use group improved from 0.96 (95% CI 0.84–1.08) to 0.44 (95% CI 0.32–0.56). The estimates of "depression" in the as-needed use group improved from 0.95 (95% CI 0.83–1.06) to 0.68 (95% CI 0.56–0.80), and the improvement in "depression" score in the proactive use group after propensity score matching was significantly greater than in the as-needed use group ($P = 0.03$, Table 4).

Both groups showed improvements in the symptoms and in the six areas of the QOL-related questionnaires, other than depression and overall QOL scale; however, no significant between-group differences were found.

DISCUSSION

This study examined the efficacy of proactive use of antihistamine eye drops throughout the pollen season in patients with SAC who have already developed symptoms, using propensity score matching to adjust for patient background bias between the two treatment groups. After propensity score matching, the proactive use group improved significantly more than the as-

Table 2 Baseline characteristics of patients in the proactive use group and as-needed use group before and after propensity score matching

Demographic characteristics	Before propensity score matching			After propensity score matching		
	Proactive use (n = 160)	As-needed use (n = 165)	P	Proactive use (n = 115)	As-needed use (n = 115)	P
Patient background						
Age, years, mean ± SD†	64.6 ± 15.2	60.0 ± 16.7	0.01*	62.9 ± 15.4	62.8 ± 15.3	0.94
Female, n (%)‡	127 (79.4)	106 (64.2)	< 0.01**	86 (74.8)	85 (73.9)	1.00
Contact lens wearing, n (%)‡	23 (14.4)	27 (16.4)	0.65	19 (16.5)	16 (13.9)	0.71
Type of antihistamine eye drops, n (%)‡						
Epinastine hydrochloride 0.1%	83 (51.9)	49 (29.7)	< 0.01**	45 (39.1)	42 (36.5)	0.86
Epinastine hydrochloride 0.05%	20 (12.5)	28 (17.0)		15 (13.0)	21 (18.3)	
Ketotifen fumarate 0.05%	0 (0.0)	1 (0.6)		0 (0.0)	0 (0.0)	
Olopatadine hydrochloride 0.1%	44 (27.5)	51 (30.9)		42 (36.5)	36 (31.3)	
Levocabastine hydrochloride 0.025%	13 (8.1)	36 (21.8)		13 (11.3)	16 (13.9)	
History of other allergic diseases, n (%)‡	76 (47.5)	86 (52.1)	0.44	57 (49.6)	59 (51.3)	0.90
Allergic rhinitis	68 (89.5)	79 (91.9)	0.79	49 (86.0)	54 (91.5)	0.39
Asthma	6 (7.9)	4 (4.7)	0.52	5 (8.8)	2 (3.4)	0.27
Atopic dermatitis	6 (7.9)	5 (5.8)	0.76	4 (7.0)	3 (5.1)	0.71
Treatment for allergic diseases, n (%)‡	83 (51.9)	85 (51.5)	1.00	57 (49.6)	59 (51.3)	0.90
Steroid eye drops	33 (39.8)	34 (40.0)	1.00	23 (40.4)	24 (40.7)	1.00
Antiallergic eye drops (mediator antireleasers)	3 (3.6)	7 (8.2)	0.33	2 (3.5)	5 (8.5)	0.44
Oral drugs	49 (59.0)	59 (69.4)	0.20	37 (64.9)	41 (69.5)	0.69
Nasal drugs	16 (19.3)	26 (30.6)	0.11	10 (17.5)	18 (30.5)	0.13
Eye wash solutions	4 (4.8)	4 (4.7)	1.00	1 (1.8)	4 (6.8)	0.36
The personality inventory in TIPI-J						
The Personality Inventory score, mean ± SD†						
Conscientiousness	4.5 ± 1.3	4.4 ± 1.1	0.40	4.5 ± 1.3	4.5 ± 1.2	0.81
Dependable, self-disciplined	4.3 ± 1.5	4.3 ± 1.4	0.96	4.3 ± 1.5	4.4 ± 1.5	0.83
Disorganized, careless	3.3 ± 1.6	3.5 ± 1.4	0.20	3.3 ± 1.6	3.3 ± 1.5	0.86
Emotional stability (neuroticism)	4.1 ± 1.3	3.9 ± 1.2	0.42	4.0 ± 1.4	3.9 ± 1.2	0.30
Anxious, easily upset	4.3 ± 1.7	4.2 ± 1.7	0.33	4.3 ± 1.8	4.1 ± 1.7	0.26
Calm, emotionally stable	4.2 ± 1.5	4.3 ± 1.3	0.82	4.3 ± 1.5	4.4 ± 1.3	0.64

Table 2 continued

Demographic characteristics	Before propensity score matching			After propensity score matching		
	Proactive use (n = 160)	As-needed use (n = 165)	P	Proactive use (n = 115)	As-needed use (n = 115)	P
Baseline JACQLQ eye symptom score						
The eye symptom score, mean ± SD[†]						
Itchy eyes	2.3 ± 0.6	2.3 ± 0.6	0.98	2.4 ± 0.6	2.3 ± 0.6	0.73
Foreign body sensation	1.5 ± 1.0	1.4 ± 1.0	0.83	1.5 ± 1.0	1.4 ± 1.1	0.62
Hyperemia	1.3 ± 1.0	1.3 ± 1.0	0.60	1.4 ± 1.0	1.3 ± 0.9	0.61
Watery eyes	1.4 ± 1.1	1.3 ± 1.0	0.60	1.4 ± 1.1	1.3 ± 1.1	0.57
Eye discharge	0.9 ± 1.0	1.1 ± 0.9	0.27	1.0 ± 1.0	1.0 ± 0.9	0.95

SD standard deviation, *JACQLQ* Japanese Allergic and Conjunctival Diseases Quality of Life Questionnaire, *TIPI-J* Ten-Item Personality Inventory

*$P < 0.05$

**$P < 0.01$

[†]The P values were determined using the Aspin–Welch t test

[‡]The P values were determined using the Fisher exact test

needed group in overall QOL scale and depression scores. The results of this study suggest that proactive use of antihistamine eye drops is a useful method for improving the QOL and mental status of patients with SAC.

This study examined the efficacy of proactive use of antihistamine eye drops throughout the pollen season. Our study was a prospective cohort study with 115 patients per group, and we adjusted for patient background bias using propensity score matching for covariates including personality. We did not limit the type of antihistamine eye drops, and we evaluated the efficacy of proactive use regardless of the type of antihistamine eye drops used. Furthermore, when comparing the efficacy of the two treatment groups, we adjusted the baseline scores and tested by ANCOVA. Similar to this study, Juniper et al. studied patients who used regular and as-needed eye drops with mast cell stabilizers (sodium cromoglycate eye drops) in a randomized, unblinded, parallel-group study [4]. They reported only 31 cases per group and limited their study to sodium cromoglycate eye drops. The results reported that the regular group had a better QOL than the as-needed group, but the symptoms were similar throughout the ragweed pollen season. These results are consistent with our study outcome. However, a detailed protocol on randomization and stringent randomization to avoid biases were unavailable because the study was published before the Consolidated Standards of Reporting Trials Statement was established. Additionally, considering the nature of drug use, direct comparison of the unblinded therapeutic effect of regular and as-needed use of drugs may cause various biases, including expectation bias that affects QOL. This necessitates the adjustment of confounding factors, including personality for proper evaluation. In our study, propensity score matching analysis on a prospective cohort study was used for the comparison of adherence or drug use in two groups. This has the advantage of reducing inherent biases in the comparison of adherence or drug use in two groups.

We also found that the proactive use group had a more significantly improved depression score in addition to the overall QOL scale than the as-needed use group. Patients with hay fever were reported to be more likely to have mood disorders such as depression and anxiety [12], and subjective symptoms such as itchy eyes

Table 3 Comparison of changes in the JACQLQ score between the proactive-use group and as-needed use group after propensity score matching using ANCOVA

Category‡	Proactive use		As-needed use		*P**
	n	Amount of change in scores from week 0 to week 2, LS mean (95% CI)	*n*	Amount of change in scores from week 0 to week 2, LS mean (95% CI)	
Eye and nasal symptoms	115	− 5.76 (− 6.62 to − 4.90)	115	− 5.34 (− 6.20 to − 4.48)	0.50
Eye symptoms	115	− 3.48 (− 3.99 to − 2.97)	115	− 3.20 (− 3.71 to − 2.69)	0.45
Itchy eyes	115	− 1.09 (− 1.22 to − 0.95)	115	− 0.99 (− 1.13 to − 0.85)	0.33
Foreign body sensation	115	− 0.62 (− 0.76 to − 0.48)	115	− 0.56 (− 0.70 to − 0.41)	0.52
Hyperemia	113	− 0.83 (− 0.96 to − 0.69)	112	− 0.69 (− 0.83 to − 0.56)	0.18
Watery eyes	113	− 0.54 (− 0.70 to − 0.38)	114	− 0.59 (− 0.74 to − 0.43)	0.66
Eye discharge	113	− 0.45 (− 0.57 to − 0.33)	114	− 0.38 (− 0.50 to − 0.26)	0.41
QOL-related questionnaires	115	− 8.03 (− 9.77 to − 6.29)	115	− 6.53 (− 8.27 to − 4.79)	0.32
Usual daily activities	115	− 3.03 (− 3.56 to − 2.50)	114	− 2.58 (− 3.10 to − 2.04)	0.23
Outdoor activities	115	− 0.95 (− 1.24 to − 0.67)	115	− 0.86 (− 1.14 to − 0.57)	0.63
Social functioning	115	− 0.92 (− 1.26 to − 0.57)	114	− 0.81 (− 1.16 to − 0.47)	0.68
Impaired sleep	115	− 0.46 (− 0.60 to − 0.32)	113	− 0.36 (− 0.50 to − 0.23)	0.33
Physical problems	115	− 0.86 (− 1.11 to − 0.61)	114	− 0.68 (− 0.93 to − 0.43)	0.30
Emotional function	115	− 1.78 (− 2.28 to − 1.28)	114	− 1.17 (− 1.67 to − 0.67)	0.09
Overall QOL Scale	109	− 0.79 (− 0.94 to − 0.64)	113	− 0.44 (− 0.59 to − 0.29)	0.002

The amount of change in the JACQLQ score from 0 to 2 weeks was compared between the proactive use group (n = 115) and as-needed use group (n = 115) after propensity score matching. Values represented least squares means (95% CI). The P values were determined using ANCOVA with baseline as an adjustment factor

JACQLQ Japanese Allergic and Conjunctival Diseases Quality of Life Questionnaire, *ANCOVA* analysis of covariance, *LS* least squares, *CI* confidence interval

*$P < 0.01$

‡Eye symptoms: symptom 01 (itchy eyes) to symptom 05 (eye discharge). Eye and nasal symptoms: symptom 01 (itchy eyes) to symptom 09 (itchy nose). Usual daily activities: QOL01 (reduced productivity at work/home) to QOL05 (decreased memory loss). Outdoor activities: QOL06 (limitation of outdoor life), QOL07 (limitation of going out). Social functioning: QOL08 (hesitation visiting friends or relatives) to QOL10 (not an easy person to be around). Impaired sleep: QOL11 (impaired sleep). Physical problems: QOL12 (tiredness) and QOL13 (fatigue). Emotional function: QOL14 (frustration) to QOL17 (unhappiness)

have been reported to reduce QOL and induce stress and sadness [13]. Proactive use of antihistamine eye drops could be effective in improving QOL during the pollen season by a reduction in the frequency of itching symptoms, and the improvement in QOL could have had an impact on the improvement in mental status. Hence, we suggest that proactive use of

Table 4 Comparison of changes in emotional function scores of JACQLQ between the proactive-use group and as-needed use group after propensity score matching

Category	Proactive use		As-needed use		P^*
	n	Amount of change in scores from week 0 to week 2, LS mean (95% CI)	*n*	Amount of change in scores from week 0 to week 2, LS mean (95% CI)	
Frustration	115	− 0.47 (− 0.62 to − 0.33)	114	− 0.28 (− 0.42 to − 0.13)	0.06
Irritability	115	− 0.48 (− 0.61 to − 0.34)	114	− 0.38 (− 0.52 to − 0.24)	0.33
Depression	115	− 0.51 (− 0.65 to − 0.36)	113	− 0.28 (− 0.43 to − 0.14)	0.03
Unhappiness	115	− 0.33 (− 0.47 to − 0.19)	114	− 0.22 (− 0.36 to − 0.08)	0.27

The amount of change in score from 0 to 2 weeks was compared between the proactive use group (n = 115) and as-needed use group (n = 115) after propensity score matching. Values represented least squares means (95% CI). The P values were determined using ANCOVA with baseline as an adjustment factor

JACQLQ Japanese Allergic and Conjunctival Diseases Quality of Life Questionnaire, *ANCOVA* analysis of covariance, *LS* least squares, *CI* confidence interval

*$P < 0.05$

antihistamine eye drops by patients with SAC could also be beneficial concerning mental status.

Many factors can influence the instillation behavior of proactive use and as-needed use. Among the many factors that influence it, personality was thought to have a strong influence. For example, it has been reported that medication compliance is associated with neuroticism and conscientiousness in patients with asthma [6–8]. In this study, the involvement of personality was also examined in patients with SAC. Before propensity score matching, the proactive use group was more likely than the as-needed use group to answer the question about conscientiousness, "disorganized, careless." The proactive use group tended to have higher scores for neuroticism and conscientiousness than the as-needed use group. Those with higher neuroticism tended to be more emotionally unstable and vulnerable to stress [14], which could affect their QOL, the outcome of this study.

Similar to previous reports [4], the current study findings showed no significant difference in subjective symptom improvement between the proactive use and as-needed use groups. The reason for this lack of significant difference was attributed to the difficulty in evaluation of the symptoms of concern at a patient-specific level, which complicated the overall assessment of each symptom question. In addition, for both proactive or as-needed use, ocular symptoms are assumed to be suppressed to a certain degree with either eye drop approach because the drops are applied so that symptoms do not become severe. These factors were considered to be the reason why no significant difference was obtained between the two groups in terms of ocular symptoms.

Although no significant between-group differences were observed for symptoms, the two groups differed significantly in QOL. The JACQLQ scores can confirm the degree of symptoms, but not the frequency of itching. Because the as-needed group always received eye drops every time they experienced itching, it is possible that the difference in the frequency of itching made a difference in QOL. In addition, if the concentration of antihistamines can be maintained throughout the pollen season by proactive use of antihistamine eye drops, this method is expected to block H_1 receptors in advance and reduce the occurrence of itching.

In contrast, the as-needed use group may feel itching at the time of eye drop application, and a certain amount of itching may occur. Furthermore, the burden of applying eye drops each time may cause mental stress. These factors may have contributed to the significant difference in QOL between the two study groups.

The study had the following limitations. It was a prospective cohort study and not a randomized controlled trial. Although propensity score matching was used to adjust for confounding factors when comparing the proactive use group with the as-needed use group, the effect of confounding factors, including factors not asked in this study, cannot be ruled out even if propensity scores were used. However, the sample size was large enough in this study to allow adjustment by propensity score matching, and the data were considered sufficiently reliable.

CONCLUSIONS

Proactive use of antihistamine eye drops is an effective means for improving the QOL of patients with SAC during the pollen season.

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REFERENCES

1. Miyazaki D, Takamura E, Uchino E, et al. Japanese guidelines for allergic conjunctival diseases 2020. Allergol Int. 2020;69:346–55.

2. Fukagawa K, Kishimoto H, Shoji J, Fukushima A, Hori Y. Effects of the compliance of anti-histamine ophthalmic solutions on Quality of Life in patients with seasonal allergic conjunctivitis using web questionnaire. Allergy no Rinsyo [Allergy Pract]. 2019;39:825–37 (in Japanese).

3. Ciprandi G, Passalacqua G, Mincarini M, Ricca V, Canonica GW. Continuous versus on demand treatment with cetirizine for allergic rhinitis. Ann Allergy Asthma Immunol. 1997;79:507–11.

4. Juniper EF, Guyatt GH, Ferrie PJ, King DR. Sodium cromoglycate eye drops: regular versus "as needed" use in the treatment of seasonal allergic conjunctivitis. J Allergy Clin Immunol. 1994;94:36–43.

5. Oshio A, Abe S, Cutrone P. Development, reliability, and validity of the Japanese version of ten item personality inventory (TIPI-J). Jpn J Pers. 2012;21:40–52.

6. Emilsson M, Berndtsson I, Lötvall J, et al. The influence of personality traits and beliefs about medicines on adherence to asthma treatment. Prim Care Respir J. 2011;20:141–7.

7. Axelsson M, Cliffordson C, Lundbäck B, Lötvall J. The function of medication beliefs as mediators between personality traits and adherence behavior

in people with asthma. Patient Prefer Adherence. 2013;7:1101–9.

8. Axelsson M, Ekerljung L, Lundbäck B, Lötvall J. Personality and unachieved treatment goals related to poor adherence to asthma medication in a newly developed adherence questionnaire—a population based study. Multidiscip Respir Med. 2016;11:42.

9. Fukagawa K, Fujishima H, Fukushima A, et al. A quality of life questionnaire for Japanese allergic conjunctival disease. Nippon Ganka Gakkai Zasshi [J Jpn Ophthalmol Soc]. 2012;116:494–502 (in Japanese).

10. Fukagawa K, Fujisima H, Takamura E, et al. Effects of prior treatment with epinastine hydrochloride ophthalmic solution between patients with seasonal allergic conjunctivitis. Allergy Meneki [Allergol Immunol]. 2015;22:1270–80 (in Japanese).

11. Samuel DG, Rentfrow PJ, William B, Swann A Jr. very brief measure of the Big-Five personality domains. J Res Personality. 2003;37:504–28. https://doi.org/10.1016/S0092-6566(03)00046-1.

12. Rodrigues J, Franco-Pego F, Sousa-Pinto B, Bousquet J, Raemdonck K, Vaz R. Anxiety and depression risk in patients with allergic rhinitis: a systematic review and meta-analysis. Rhinology. 2021;59:360–73.

13. Marshall PS, Colon EA. Effects of allergy season on mood and cognitive function. Ann Allergy. 1993;71:251–8.

14. Costa PT Jr, McCrae RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) Professional Manual. Odessa, FL: Psychological Assessment Resources; 1992.