

Effects of Topical Application of Ibudilast for Seasonal Allergic Conjunctivitis in Patients Wearing Soft Contact Lenses

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Purpose: To assess the influence of topical application of ibudilast for seasonal allergic conjunctivitis in patients wearing soft contact lenses (SCLs).

Materials and Methods: There were 16 SCL wearers (32 eyes) with allergic conjunctivitis due to cedar pollen, who were studied from February to April 2007. Before enrollment, informed consent to participation in this study was obtained from all subjects. A frequent replacement SCL (2Week Pure) was worn for 2 weeks, and ibudilast was applied topically four times daily during this period. The severity of allergic symptoms and the severity of SCL-related symptoms were assessed by scoring using two questionnaires, and before and after topical application of ibudilast results were compared. The severity of objective ocular findings was also scored and compared in the same way. After the final examination, the SCLs were collected and immersed in physiologic saline. Then morphologic changes and drug adsorption were investigated.

Results: Among the allergic symptoms, itching and a dry sensation improved after topical application of ibudilast ophthalmic solution (both $P < 0.05$). Phlyctenular conjunctivitis was noted in one eye after topical application, but there were no significant differences of SCL-related symptoms and objective ocular findings between before and after application. There were also no morphologic changes of the contact lenses, and the ibudilast concentration in the lenses was below the detection limit.

Conclusions: These results suggest that topical application of ibudilast while using 2Week Pure lenses can improve subjective symptoms without influencing drug adsorption or lens morphology.

Key Words: Ibudilast—Allergic conjunctivitis—Soft contact lens—Pollinosis.

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Although it is recommended that ophthalmic solutions should, in principle, be avoided while wearing soft contact lenses (SCLs),^{1–3} there are actually many SCL wearers who use ophthalmic solutions. The number of patients with seasonal allergy, including pollinosis, has been increasing.⁴ Cedar pollen is one of the most common allergen in Japan. At present, the number of

SCL wearers is increasing, and it is not uncommon for allergic conjunctivitis to occur in these SCL wearers.

It has been reported that the use of a topical anti-allergic drug during SCL wear did not cause adverse reactions, such as keratoconjunctival disorders, and that little drug or preservative was adsorbed by the lens.^{5–8} Whether desirable results are obtained with all types of lenses has not been verified yet while the kind of the lens is in the increasing tendency.

Soft contact lenses are generally composed of hydrogels. It has been shown in recent years that most of the Food Drug Administration group IV SCLs, which are among the main frequent-replacement SCLs or disposable SCLs, are readily influenced by the external environment, because these anionic lenses readily incorporate dissolved substances or show morphologic changes. On the other hand, we have reported that a zwitterionic SCL (which also belongs to group IV and contains both anions and cations) was morphologically stable and showed little drug uptake release after topical application of an ophthalmic solution.^{9–11}

In this study, we assessed the influence of ibudilast ophthalmic solution (an antiallergic agent for seasonal allergic conjunctivitis) on a zwitterionic SCL from the standpoint of changes in subjective symptoms, objective findings, and changes of the lens itself.

MATERIALS AND METHODS

The subjects comprised 16 SCL wearers (32 eyes) who had allergic conjunctivitis due to cedar pollen. This study was approved by the Ethical Committee of our hospital. Informed consent to participation was obtained from all subjects after they fully understood the objectives and procedures. The study period was 3 months (from February 1 to April 30, 2007). The test contact lens was a 2Week Pure (Seed Co., Ltd., Tokyo, Japan), which is a zwitterionic frequent-replacement SCLs. According to the manufacturer's directions, these lenses were worn in both eyes daily for 2 weeks. Every subject followed the official protocol for lens care distributed by the manufacturer. They used multipurpose solution ReNu MultiPlus (Bausch & Lomb, Rochester, NY), consisting of biguanide polyhexanide. During this period, ibudilast ophthalmic solution (Eyevinal; Banyu pharmaceutical, Co., Ltd., Tokyo, Japan) was applied to both eyes four times daily. After completion of the final examination, the used lenses were collected for analysis between approximately 1 hr and 3 hr after final administration. Other anti-allergic drugs including the internal medicine were prohibited for the experimental period.

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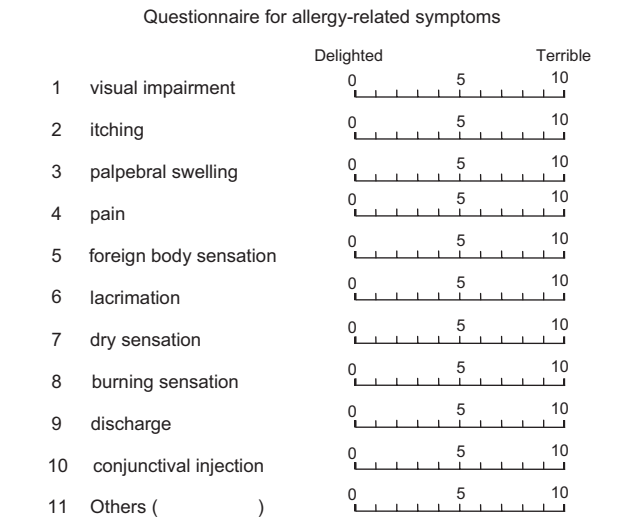


FIG. 1. A copy of questionnaire for allergy-related symptoms. This chart was translated in English.

The items investigated were (1) objective findings including lens-fitting pattern, (2) a questionnaire survey of allergy-related symptoms, (3) a questionnaire survey of contact lens-related symptoms, and (4) analysis of the used lenses. The results were compared between before and after topical application of ibudilast. In the questionnaire surveys, the severity of each symptom was scored on a visual analog scale and was compared between before and after topical application. The score was set at 0 points for the mildest symptom and 10 points for the most severe symptom.

Among the objective ocular findings, the severity of findings in the anterior segment was scored according to the New Clinical Evaluation Criteria and Severity Classification for Allergic Conjunctival Diseases of the Japanese Ocular Allergy Study Group,¹² and the results were compared between before and after topical application of ibudilast. Ophthalmologists at our hospital performed a lens-fitting test on the first day of lens wearing, with topical application of the ophthalmic solution, and again after 2 weeks of wearing the lenses.

The items in questionnaire survey about allergy-related symptoms included visual impairment, itching, palpebral swelling, pain, foreign body sensation, lacrimation, dry sensation, burning sensation, discharge, and conjunctival injection. The severity of each symptom was scored for evaluation (Fig. 1).

The items in questionnaire survey about contact lens-related symptoms were as follows: dirt (surface deposition), blurring, discomfort while wearing, difficulty in removal, dislocation of lenses, and difficulty in seeing. The severity of each symptom was scored for evaluation (Fig. 2).

For analysis of the used lenses, the lens being worn on the day of final observation was collected after the final examination and was immersed in physiologic saline as previously reported.⁹ Then, it was used to assess morphologic changes and absorption of ibudilast by the lens analysis method with a dimension analyzer (Optimec, Ltd., Malvern, UK) and high-performance liquid chromatography (JASCO Corporation, Tokyo, Japan). The items evaluated for the collected lenses were the diameter after wearing, the curvature and power, the morphology, and the adsorption of ibudilast. After each lens was immersed for 24 hr in 2 mL of

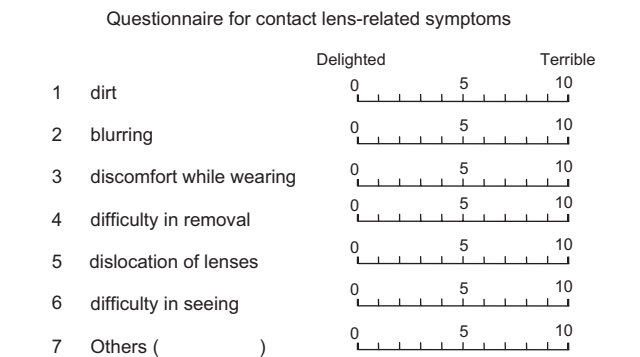


FIG. 2. A copy of questionnaire for allergy-related symptoms. This chart was translated in English.

methanol, the extract was used for measurement of ibudilast by high-performance liquid chromatography.

SPSS software (SPSS for Windows, version 11.0; SPSS Inc, Chicago, IL) was used for statistical analysis. A value of *P* less than 0.05 was considered significant, and all statistical comparisons were made with the Wilcoxon signed-ranks test.

RESULTS

1. On ocular examination, no corneal findings were noted in any of the patients at the time of examination before the study, so all of them were able to participate in this study. No corneal findings were observed either at the time of final medical examination. The following findings were noted during the observation period: conjunctival injection in 22 of 32 eyes before administration, papillary hyperplasia of the palpebral conjunctiva in a 31 of 32 eyes (Table 1). However, these objective signs showed no differences with regard to the number of eyes affected and the severity after topical application. There were also no significant differences of the scores. In addition to these findings, mild edema of the palpebral conjunctiva was noted in one patient (two eyes) before topical application. However, this patient was enrolled in the study because the edema was considered to be mild enough for use of SCLs. After starting topical application of ibudilast, conjunctival edema resolved in both eyes. On the other hand, Phlyctenular conjunctivitis was noted in one patient (one eye) at the final observation. Therefore, use of contact lenses was discontinued in this patient, and topical application of 0.1% fluorometholone ophthalmic solution (Flumetholon 0.1%, Santen Pharmaceuti-

TABLE 1. Ocular Findings Noted During the Observation Period (n = 16)

	Before instillation (mean ± SD)	Final observation (mean ± SD)	P (Wilcoxon signed-ranks test)
Conjunctival injection	0.78 ± 0.02	0.63 ± 0.02	0.1290
Papillary hyperplasia of the palpebral conjunctiva	1.31 ± 0.02	1.22 ± 0.02	0.3657

Other findings, mild edema of the palpebral conjunctiva: two eyes; phlyctenular conjunctivitis: one eye.

Although conjunctival injection and papillary hyperplasia were shown, there were no changes in the number of eyes and the scores.

SD indicates standard deviation.

TABLE 2. The Scores for Allergy-Related Symptoms Evaluated by a Questionnaire Survey ($n = 16$)

	Before instillation (mean $\pm$ SD)	Final observation (mean $\pm$ SD)	<i>P</i> (Wilcoxon signed-ranks test)
Visual impairment	1.25 $\pm$ 0.09	1.44 $\pm$ 0.11	0.7159
Itching	4.19 $\pm$ 0.17	2.25 $\pm$ 0.17	0.0165 ^a
Palpebral swelling	1.50 $\pm$ 0.13	1.00 $\pm$ 0.13	0.2623
Pain	0.94 $\pm$ 0.10	0.50 $\pm$ 0.06	0.2207
Foreign body sensation	3.31 $\pm$ 0.18	2.19 $\pm$ 0.16	0.0915
Lacrimation	1.94 $\pm$ 0.21	1.56 $\pm$ 0.18	0.8335
Dry sensation	4.50 $\pm$ 0.22	2.31 $\pm$ 0.13	0.0120 ^a
Burning sensation	0.63 $\pm$ 0.12	0.25 $\pm$ 0.05	0.6803
Discharge	2.31 $\pm$ 0.16	2.44 $\pm$ 0.20	0.9635
Conjunctival injection	3.44 $\pm$ 0.23	1.94 $\pm$ 0.17	0.0980

The scores for itching and dryness of the eyes decreased significantly after instillation of ibudilast eye drops compared with before its instillation.

^a $P < 0.05$.

SD indicates standard deviation.

cal, Co. Ltd., Osaka, Japan) four times daily was started. As a result, the Phlyctenular conjunctivitis disappeared after approximately 1 week of treatment. The lens-fitting pattern was classified as “parallel” both before and after topical application of ibudilast in all patients.

- In the evaluation of allergy-related symptoms, the scores for itching and dryness of the eyes showed statistically significant improvement after topical application of ibudilast compared with before its application (Wilcoxon signed-ranks test, $P = 0.0165$, $P = 0.0120$, respectively) (Table 2).
- In the evaluation of lens-related symptoms, the scores for each symptom showed no significant differences between before and after application of ibudilast (Table 3).
- Analysis of the collected lenses showed that they met the standards with respect to diameter, curvature, and power. The lenses showed no morphologic changes in any parameter (Fig. 3). In addition, the adsorption of ibudilast by the lenses was below the detection limit.

DISCUSSION

The safety of SCLs may be decreased by potential morphologic changes due to incorporation of drug ingredients or the influence of the pH of an ophthalmic solution. Furthermore, topical application of an ophthalmic solution while wearing SCL may alter the

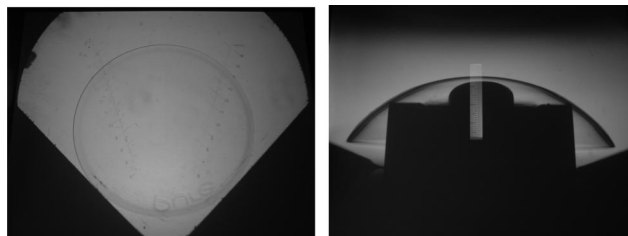
TABLE 3. The Scores for Contact Lens-Related Symptoms Evaluated by a Questionnaire Survey ($n = 16$)

	Before instillation (mean $\pm$ SD)	Final observation (mean $\pm$ SD)	<i>P</i> (Wilcoxon signed-ranks test)
Dirt (surface deposition)	1.67 $\pm$ 0.15	1.53 $\pm$ 0.14	0.9517
Blurring	1.87 $\pm$ 0.16	2.07 $\pm$ 0.15	0.5721
Discomfort while wearing	2.20 $\pm$ 0.18	1.93 $\pm$ 0.14	0.5695
Difficulty in removal	1.87 $\pm$ 0.16	1.00 $\pm$ 0.11	0.3216
Dislocation of lenses	1.87 $\pm$ 0.16	1.27 $\pm$ 0.16	0.3598
Difficulty in seeing	1.20 $\pm$ 0.12	1.67 $\pm$ 0.12	0.4410

Other symptom, foreign body sensation: one eye at both initial and final observation.

There were no changes in the scores for all symptoms before and after instillation of ibudilast eye drops.

SD indicates standard deviation.

**FIG. 3.** The example images of used contact lenses collected after the final examination. No morphologic changes were seen in lenses.

pharmacokinetics of the solution itself, so that development of efficacy may be inhibited depending on the drug. Actually, some reports showed possibility of side effects.^{13,14}

Among the various SCLs that are presently on the market, group IV lenses are the most popular. Most of these lenses are made from anionic material, because there are ionic groups in the lens material such as carboxyl groups. Anionic SCLs can maintain a high water content and good morphology by repelling anions but have the disadvantages of protein adsorption to the lens due to electrical interaction with protein in tears and morphologic changes due to the effects of the pH and salt concentration. On the other hand, the group IV zwitterionic SCL used in this study is safer because of the following characteristics. Because there are both anionic and cationic groups in the lens material, if interactions between the ions are controlled, protein adsorption to the lens surface will be inhibited and morphologic changes related to alterations of the pH and salt concentration (a disadvantage of conventional ionic SCLs) will also be prevented.

In a previous study, we observed excellent morphologic stability and little drug incorporation/release during an in vitro study on interactions between Ketotifen Fumarate ophthalmic solution (Zaditen, Zaditen UD, Novartis Pharma KK, Tokyo, Japan) and benzalkonium chloride (the preservative contained in the ophthalmic solution) and a zwitterionic SCL.^{9–11} Also, an in vitro study was performed in which 8-hr immersion of the zwitterionic SCL in the ibudilast ophthalmic stock solution was repeated 14 times to mimic 8 hr of wear daily for 2 weeks.¹⁵ As a result, no morphologic changes occurred, and there was little drug incorporation, release, or adsorption. On the other hand, all three types of silicone hydrogel lenses, O₂ Optix, Acuvue Advance, and Acuvue Oasis, used in the in vitro experiment showed considerable incorporation, release, and adsorption. In addition, an increase of lens diameter was noted, whereas the diameter of the 2Week Acuvue decreased. Thus, even for SCLs of the same Group, whether morphologic changes were induced by topical application of an ophthalmic solution was determined by the lens material. Interactions with drugs were also considered to depend on the lens material. If a lens shows deformity on the cornea and conjunctiva due to topical application of an ophthalmic solution, there is a high likelihood of both inappropriate lens fitting and complications, such as sticking to the cornea, lens displacement, keratoconjunctival epithelial damage, and visual impairment. It is necessary to pay special attention to the combination of lens material and ophthalmic solution when a solution is used by an SCL wearer.

Based on these findings, we have performed the present in vivo study. As a result, topical application of ibudilast ophthalmic solution had no influence on the morphology of the zwitterionic SCL, and absorption of ibudilast by the lens was not observed. The

results of this in vivo study indicate that the topical application of ibudilast ophthalmic solution is safe in persons wearing this zwitterionic SCL. On the other hand, it is a general concern that use of an ophthalmic solution while wearing SCL will reduce its efficacy because of incorporation of the ingredients into the lens. However, improvement of itching and dryness were noted due to administration of ibudilast ophthalmic solution in patients wearing this zwitterionic SCL, so it is considered that there is little likelihood of the pharmacologic effect of ibudilast being inhibited. On the other hand, when ibudilast was applied topically in patients wearing 2Week Pure SCLs, Phlyctenular conjunctivitis occurred in one patient (one eye). Because this patient had a history of the symptom and the steroid ophthalmic solution was effective, it was not classified as a serious adverse event. Also, its relationship to lens wear, interaction between lens care solution, and lens or topical application of ibudilast was unclear.

The results of this study suggest that topical application of ibudilast in patients wearing zwitterionic SCLs can improve allergy-related symptoms, such as itching and dry sensation, without having an influence on drug absorption or lens morphology. These results of the present study might be limited to the lens type researched, and not be presumed to other lens types, for example, silicone hydrogel lenses.

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