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Improvements in Signs and Symptoms of Dry Eye after Instillation of 2% Rebamipide

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Purpose: Because dry eye greatly reduces quality of life, this study aimed to examine rebamipide instillation in patients with dry eye and assess the improvement of signs and symptoms as evaluated with the Ocular Surface Disease Index, which is the most popular index and is highly reliable.
Methods: From June 2013 through January 2014, we examined 50 eyes of 25 patients with dry eye (6 men and 19 woman) at our institution. Dry eye was diagnosed on the basis of the presence of symptoms, tear dynamics, and ocular surface abnormalities according to the Japanese criteria for dry eye. Before being enrolled, all patients underwent ocular surface health assessment, including history interviews, and completed the Ocular Surface Disease Index questionnaire. Patients received 2% rebamipide ophthalmic solution 4 times daily for 4 weeks. Signs and symptoms were analyzed before and 4 weeks after rebamipide administration. Tear dynamics, tear break-up time, and ocular surface abnormalities were measured and compared between before and 4 weeks after rebamipide administration.
Results: Of the 25 patients, 9 had definite dry eye and 16 had probable dry eye. Tear break-up time and the fluorescein staining score significantly improved after 4 weeks. However, no significant change was observed for the Schirmer test I and the lissamine green staining score.
Conclusions: The administration of 2% rebamipide 4 times daily for 4 weeks improves the signs and symptoms of dry eye and improves patients' quality of life. (J Nippon Med Sch 2015; 82: 229–236)

Key words: dry eye, rebamipide, Ocular Surface Disease Index (OSDI), symptoms, signs

Introduction

According to Japanese diagnostic criteria[1], dry eye is defined as a chronic multifactorial disease of the tears and keratoconjunctival epithelium and is accompanied by ocular discomfort and visual dysfunction. The mainstream treatment for dry eye is eye drops. The first-line treatment in the United States is cyclosporine instillation, whereas the drugs of first choice in Japan are hyaluronate ophthalmic solutions. Now marketed in Japan, however, are diquafosol ophthalmic solution (Diquas Ophthalmic Solution 3%; Santen Pharmaceutical Co., Ltd., Osaka, Japan) and rebamipide ophthalmic solution (Mucosta ophthalmic suspension UD2%; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). Both ophthalmic solutions induce mucin production[2,3].

Of the 2 agents, rebamipide has a long history of use and was originally launched in 1990 as an oral medication for repairing the gastric mucosa by stimulating mucin production[4,5]. Rebamipide also exerts further effects on the ocular surface cells. Experiments have shown that rebamipide increases the amount of mucinlike substances in the conjunctival goblet cells and in keratoconjunctival epithelial cells in vitro and in vivo[2,6,7]. In addition, as a clinical topical agent rebamipide has been shown to increase the number of mucin-containing goblet cells[8]. The utility of rebamipide ophthalmic solution as a therapeutic

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agent for dry eye has been clearly demonstrated in a phase III study[9] and a multicenter study[10]. Stable expression of mucin is a novel concept in the treatment of dry eye, and recent studies have shown that its use can be extremely effective[11,12]. Other studies have shown that rebamipide, in addition to causing an increase in mucin production, also promotes gastric ulcer healing through prostaglandin production in the gastric mucosa[13], inhibits esophageal and gastric cytokines and chemokines, and has anti-inflammatory effects[14]. Because dry eye is an inflammation of the ocular surface[15], administration of rebamipide should have an efficacious anti-inflammatory effect for its treatment.

Because dry eye is a disease associated with such problems as eye pain, burning pain, foreign body sensation, and irritation[16], it greatly reduces quality of life[17,18]. Recent reports have indicated that quality of life is more reduced in patients who have moderate-to-severe dry eye than in patients who have severe angina or hip fracture or are undergoing dialysis[19,20]. Thus, a major goal in the treatment of dry eye is to improve symptoms[1]. However, as a review has shown[18], the signs and symptoms of patients with dry eye often lack correlation. In other words, more than signs must be treated for the proper medical care of patients with dry eye. Therefore, to survey symptoms, clinicians have used a variety of questionnaires, among which the most popular and highly reliable is the Ocular Surface Disease Index (OSDI)[21]. In the present study, we examined rebamipide instillation in patients with dry eye and assessed the improvement of signs and symptoms as evaluated with the OSDI.

Materials and Methods

This study was an open-label, single-arm study that followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Nippon Medical School Hospital (approval number, 224019). Before subjects were enrolled the study was registered at the Japanese University Hospital Medical Information Network Clinical Trials Registry (clinical trial identifier: UMIN000008873; accessed September 7, 2012).

From June 2013 through January 2014, we examined 50 eyes of 25 patients (6 men and 19 women) with dry eye at the Department of Ophthalmology, Nippon Medical School. Patients received 2% rebamipide ophthalmic solution 4 times daily for 4 weeks. Before and 4 weeks after rebamipide was administered signs and symptoms were analyzed. Patients were excluded if they had any ocular surface diseases other than dry eye or had Sjögren syndrome, which can necessitate surgical treatment, such as punctal occlusion, as well as eye drops. Of these 25 patients, 10 had earlier been given prescriptions for a hyaluronate ophthalmic solution (Hyalein, Santen Pharmaceutical Co., Ltd.) 4 times daily by a previous physician and were allowed to continue receiving sodium hyaluronate concomitantly with the rebamipide. Sodium hyaluronate was administered for at least 3 months. The patients' mean (±SD) age was 62.0±16.6 years (range, 23 to 82 years). Dry eye was diagnosed according to the Japanese Definition and Diagnosis of Dry Eye 2006 criteria that evaluate the presence of symptoms, tear dynamics, and ocular surface abnormalities. Tear dynamics were assessed with the Schirmer test I and tear break-up time. If either of these tests was positive (Schirmer test ≤5 mm; break-up time ≤5 seconds), the tear dynamics were considered abnormal. Ocular surface abnormalities were identified through positive vital staining with fluorescein or lissamine green. The degree of staining in the temporal and nasal conjunctiva and the cornea, which were divided into 3 parallel sections, was recorded and quantified on a score of 0 to 3 points. Thus, the maximum score that could be obtained from the staining of 1 eye was 9 points. Measurements of both eyes were used to calculate the variables. If either type of staining (fluorescein staining score [FSS] or lissamine green staining score [LSS]) was positive, the ocular surface was considered to be abnormal. Among patients with symptoms, those with abnormal tear dynamics and ocular surface were considered to have definite dry eye, and those with only 1 positive test were considered to have probable dry eye.

Table 1 Ocular Surface Disease Index©

a. Eyes that are sensitive to light
b. Eyes that feel gritty
c. Painful or sore eyes
d. Blurred vision
e. Poor vision
f. Reading
g. Driving at night
h. Working with a computer or bank machine
i. Watching television
j. Windy conditions
k. Places or areas with low humidity (very dry)
l. Areas that are air conditioned

Before being enrolled, all patients underwent ocular surface health assessment, including history interview, and completed the OSDI questionnaire (**Table 1**)[21].

The 12 items of the OSDI questionnaire were graded on a scale of 0 to 4. A grade of 0 indicates none of the

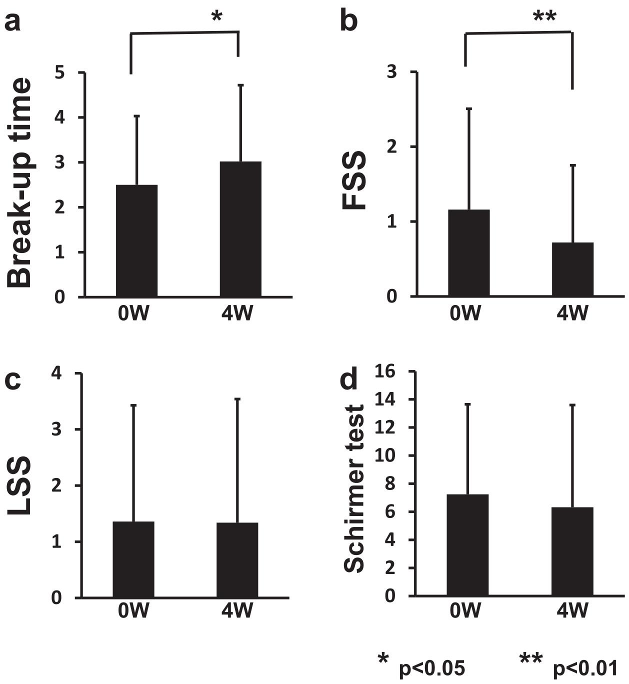

Fig. 1 Changes in objective signs as a result of rebamipide treatment
a, tear break-up time; **b**, fluorescein staining score (FSS); **c**, lissamine green staining score (LSS); **d**, Schirmer test I.

time, 1 indicates some of the time, 2 indicates half of the time, 3 indicates most of the time, and 4 indicates all of the time. The total OSDI score was calculated with the following formula: OSDI = (sum of scores for all questions answered 100) × 100 / (total number of questions answered) × 4. The OSDI was scored on a scale of 0 to 100, with higher scores representing greater disability. Subscale scores were computed similarly, with only the questions from each subscale used to generate its own score.

Statistical Analysis

The profiles obtained before and 4 weeks after the administration of rebamipide were analyzed with a paired *t*-test for the signs and a Wilcoxon signed-rank test for the symptoms. The analysis was performed with the program Statmate III (ATMS Co., Ltd., Tokyo, Japan).

Result

The Japanese Definition and Diagnosis of Dry Eye 2006 criteria indicated that 9 of the 25 patients had definite dry eye and 16 had probable dry eye.

Examination of Dry Eye

From before to 4 weeks after rebamipide was administered the break-up time (**Fig. 1a**) improved significantly from 2.5±1.56 to 3.02±1.73 (*P*=0.029), and the FSS (**Fig. 1b**) improved from 1.19±1.36 to 0.75±1.04 (*P*=0.005). No significant improvement, however, was seen for the LSS (**Fig. 1c**) (from 1.42±2.09 to 1.27±2.13 [*P*=0.28]) or the Schirmer test (**Fig. 1d**) (from 7.17±6.5 to 6.23±7.42 [*P*=0.13]).

In patients with definite dry eye, the FSS (**Fig. 2b**) improved significantly (*P*=0.018) and the LSS (**Fig. 2c**) showed a tendency to improve (*P*=0.052). However, the break-up time (**Fig. 2a**) showed no improvement (*P*=0.421). In patients with probable dry eye, significant improvements were observed for both the break-up time (*P*=0.003) (**Fig. 2e**) and the FSS (*P*=0.045) (**Fig. 2f**).

In patients who received only rebamipide, improvements were seen in both the break-up time (**Fig. 3a**) (*P*=0.003) and the FSS (**Fig. 3b**) (*P*=0.01). In patients who received both sodium hyaluronate and rebamipide, however, no results showed improvement (**Fig. 3e–h**).

OSDI Score

From before to 4 weeks after rebamipide administration the OSDI score showed a significant improvement from 39.0±19.8 to 26.0±20.2 (*P*<0.01, **Fig. 4a**). In patients with definite dry eye the OSDI score improved, but not to a significant extent, from 43.5±25.9 to 35.2±23.5 (*P*=0.21, **Fig. 4b**). However, in patients with probable dry eye the OSDI score improved significantly from 36.5±27.9 to 20.9±28.1 (*P*<0.01, **Fig. 4c**). From before to 4 weeks after rebamipide administration, significant improvements in score were observed for 5 OSDI items: b, c, f, k, and l (**Fig. 5**). The OSDI score showed a significant improvement (*P*<0.01) from 38.2±21.4 to 19.85±18.7 in patients receiving only rebamipide (**Fig. 6a**) and a nonsignificant change from 40.7±15.9 to 36.6±19.9 (*P*=0.26) in patients receiving both sodium hyaluronate and rebamipide (**Fig. 6b**).

Discussion

The quinolinone derivative rebamipide was developed as a therapeutic agent for gastric ulcer[23,24]. Its ability to promote the healing of injuries has been demonstrated in a rat model of gastric ulcers[23,24]. Although rebamipide derives its efficacy by promoting mucin production in the gastric mucosa[4], it also increases keratoconjunctival mucin expression and the number of conjunctival goblet cells on the ocular surface in rabbits[25]. Mucin is an important wetting agent for the ocular surface and contributes to the tear film stability[26,27]. The effectiveness of rebamipide, which induces mucin expression, as a therapeutic agent for dry eye has been demonstrated in a large number of patients[10].

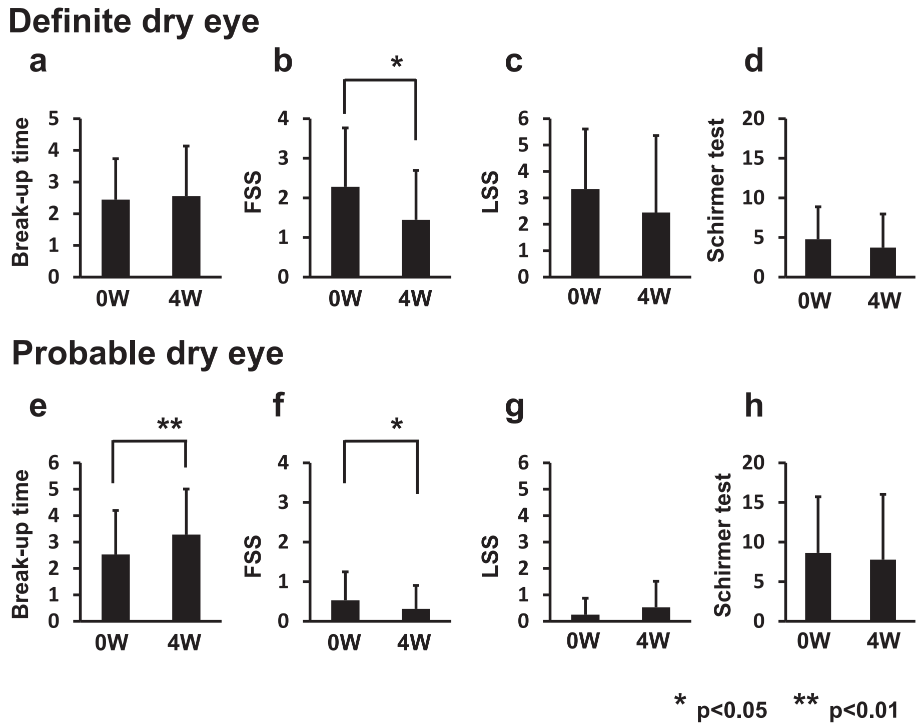

Fig. 2 Changes in objective signs in patients with definite/probable dry eye as defined by the Japanese criteria
Definite dry eye: **a**, break-up time; **b**, FSS; **c**, LSS; **d**, Schirmer test I. Probable dry eye: **e**, Break-up time; **f**, FSS; **g**, LSS; **h**, Schirmer test I.

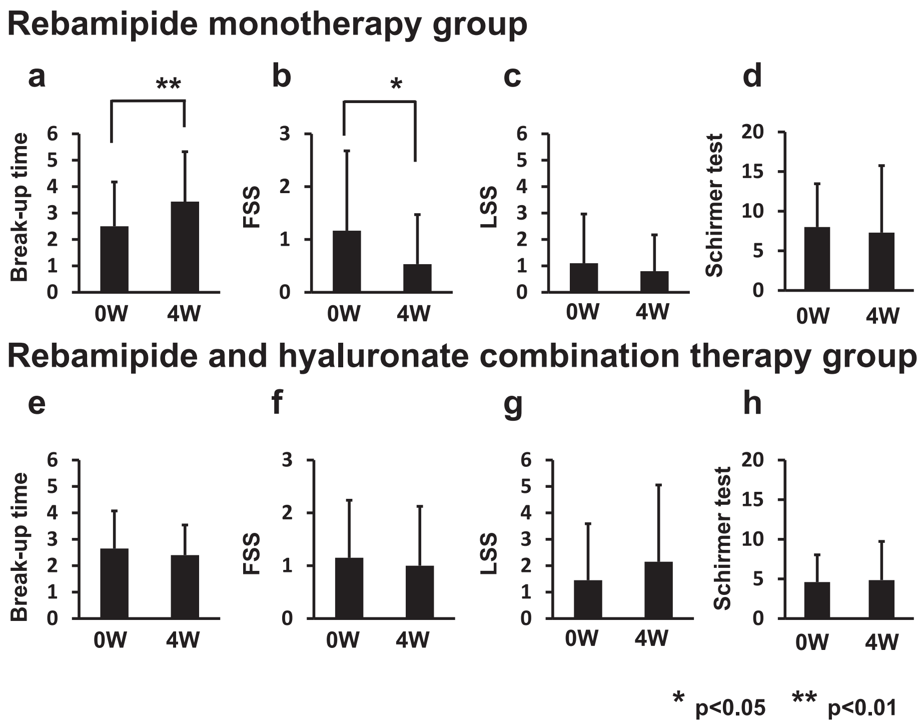

Fig. 3 Changes in objective signs in the rebamipide monotherapy group and the rebamipide and hyaluronate combination therapy group
Rebamipide monotherapy group: **a**, Break-up time; **b**, FSS; **c**, LSS; **d**, Schirmer test I. Rebamipide and hyaluronate combination therapy group: **e**, Break-up time; **f**, FSS; **g**, LSS; **h**, Schirmer test I.

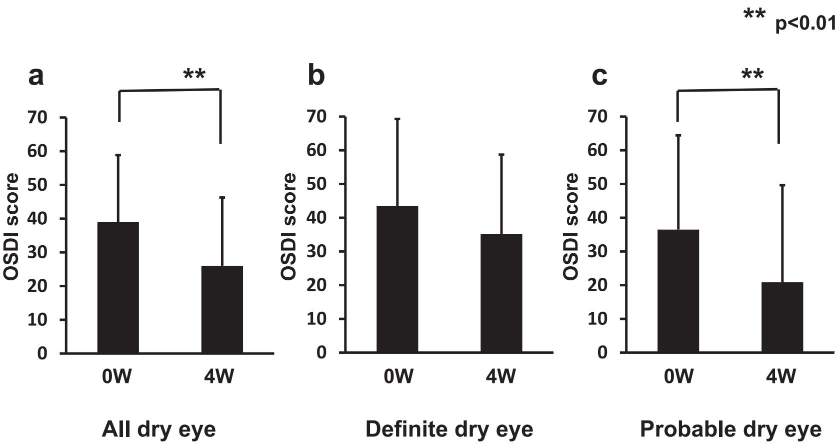

Fig. 4 Changes in the OSDI score as a result of rebamipide treatment
a, change in the OSDI score in the overall patient population; **b**, changes in patients with definite dry eye; **c**, changes in patients with probable dry eye.

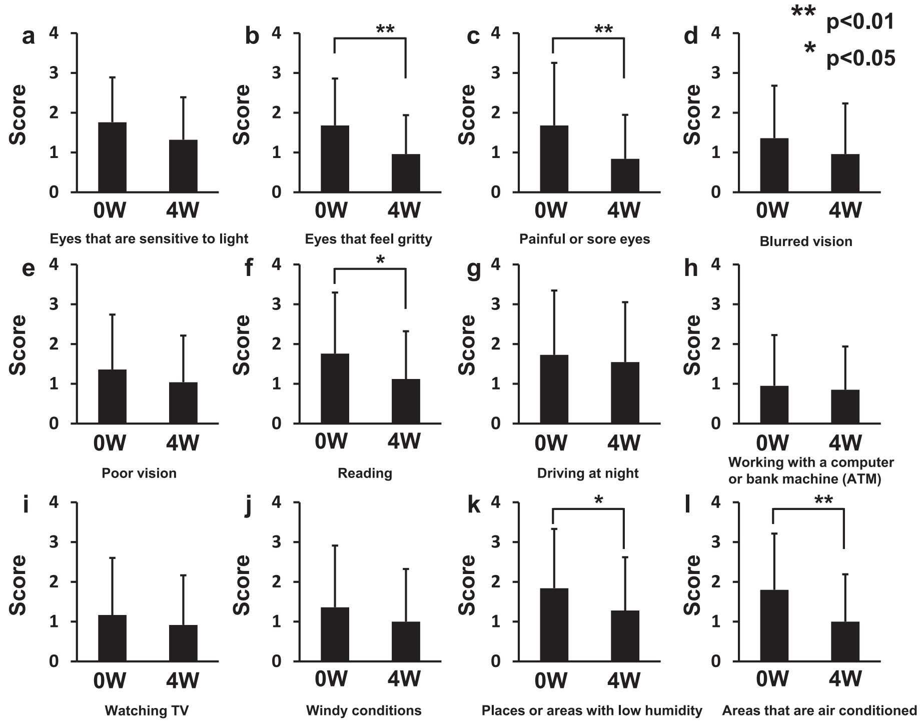

Fig. 5 Changes in scores of individual OSDI items
a, Eyes that are sensitive to light; **b**, Eyes that feel gritty; **c**, Painful or sore eyes; **d**, Blurred vision; **e**, Poor vision; **f**, Reading; **g**, Driving at night; **h**, Working with a computer or bank machine; **i**, Watching TV; **j**, Windy conditions; **k**, Places or areas with low humidity (very dry); **l**, Areas that are air conditioned.

In the present study, our overall analysis demonstrated improvements of both break-up time and the FSS. However, a previous study found significant improvements in break-up time, the FSS, and the LSS but no improvement in the Schirmer test[9]. We found similar results in our study when we performed a direct comparison of the individual scores. A stratified analysis showed improvement of only the FSS in patients with definite dry eye but showed improvement of both break-up time and the FSS in patients with probable dry eye. A study that examined patients with Sjögren syndrome found similar improvements in the FSS and the LSS but not in break-up time[28]. While rebamipide is suggested by these data to improve the FSS, its effect on break-up time was unsatisfactory in patients with severe dry eye, such as those with decreased tear amounts. The data of these studies

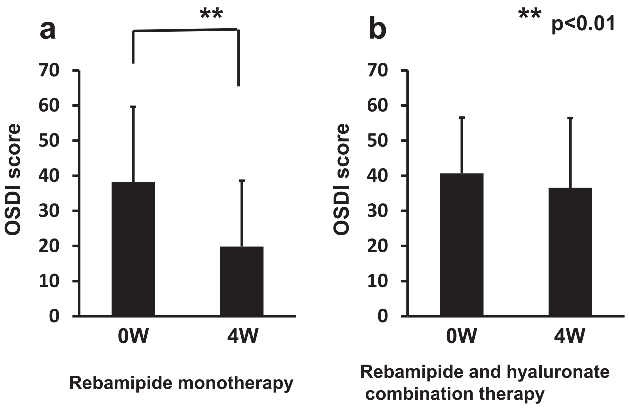

Fig. 6 Changes in the OSDI score in the rebamipide monotherapy group and the rebamipide and hyaluronate combination therapy group
a, change in the OSDI score in rebamipide monotherapy group; **b**, change in the OSDI score in the rebamipide and hyaluronate combination therapy group.

also showed an improvement in the LSS[9,28] which was to a greater than that in our study. A possible reason for this difference is our study excluded patients with Sjögren syndrome. Nonetheless, the LSS in patients with definite dry eye (3.33) was larger than that in patients with probable dry eye (2.44) and showed a tendency to improve (P=0.052). Moreover, these data indicate that the break-up time is more likely to improve in patients with mild dry eye.

Our present study also compared changes in patients who received only rebamipide and patients who received both rebamipide and sodium hyaluronate. Although both break-up time and the FSS improved in patients receiving rebamipide alone, neither improved significantly in patients receiving both rebamipide and sodium hyaluronate. Of the 10 patients who received both rebamipide and sodium hyaluronate, which had been prescribed by a previous physician, 5 had definite dry eye and 5 had probable dry eye. Because patients who received both rebamipide and sodium hyaluronate were not patients with severe dry eye, the above discussion based on the difference in the tear amounts does not apply here. Thus, the cause of the differences in the effect of break-up time and FSS between patients receiving only rebamipide and those receiving both rebamipide and sodium hyaluronate remain unknown. Our present study and the previous report that rebamipide ophthalmic solution improves both signs and symptoms[9] suggest that rebamipide ophthalmic solution is a sensible choice for the treatment of dry eye. Moreover, because the addition of rebamipide ophthalmic solution provided no improvement in patients for whom sodium hyaluronate alone had been ineffective, rebamipide ophthalmic solution, rather than a combination therapy, probably should be considered for such patients.

We are unaware of any earlier study that has used the OSDI to assess the improvement of symptoms in patients treated with rebamipide. The effects of rebamipide on foreign body sensation, dryness sensation, photophobia, eye pain, and blurred vision have been examined[10] and compared with the effects of artificial tears[29] or 0.1% sodium hyaluronate[9]. However, in these studies the OSDI was not used to evaluate symptoms. These studies[9,10,29] showed that rebamipide is efficient for improving symptoms despite not improving results of the Schirmer test, which is similar to our data. Another study has found that 5 variables—foreign body sensation, dryness sensation, photophobia, eye pain, and blurred vision—improved significantly by 4 weeks after administration of rebamipide. However, once again, this study also did not use the OSDI[28].

While various types of survey questionnaires are used for patients with dry eye, the OSDI is comparable to the Impact of Dry Eye on Everyday Life questionnaire (IDEEL)[30] in that both have been validated and reported to be reliable questionnaires[31]. Compared with the IDEEL, which has 57 question items, the OSDI consists of only 12 question items, and thus is an easy tool to use clinically[31]. Due to the low correlation between the signs and symptoms of dry eye[18], medical interviews that specifically target subjective symptoms are also important[32]. In recent years, the United States Food and Drug Administration has required the correct use of patient-reported outcome measures, such as those that reflect patients' quality of life, when assessing the effects of drugs in clinical trials[33]. In that respect, the OSDI, which contains items concerning vision-related functions, ocular symptoms, and environmental triggers, has been shown to reflect valuable patient-reported outcome measures in clinical trials and ophthalmic clinical practice[16,31,32]. Given the above, in the present study we assessed all items in the OSDI to evaluate the symptoms. We showed both significant improvements in foreign body sensation and eye pain, which are among the 5 items (foreign body sensation, dryness sensation, photophobia, eye pain, and blurred vision) that have been investigated in previous studies[9,10,28,29]. In addition, we showed significant improvements in difficulties associated with reading, places of low humidity, or areas that are air conditioned. However, we should note that because most of our subjects were relatively elderly persons (mean age, 62 years) living in central Tokyo, the likelihood was decreased that the OSDI scores would differ with respect to driving and working with a computer. For the treatment of dry eye, improving signs is extremely important. However, in some patients symptoms do not improve despite signs improving. The present results confirm that rebamipide improves signs as well as symptoms. Rebamipide is potentially a drug of choice for patients who have no improvement in symptoms despite improvements in signs after treatment with another drug.

Inflammation is deeply involved in the pathology of dry eye. Inflammation reduces tear film stability, resulting in corneal and conjunctival impairments[15]. In fact, increased levels of inflammatory cytokines have been reported in the tear film of patients with dry eye[34,35]. Rebamipide is a drug of great interest from an anti-inflammation viewpoint, because in addition to having an anti-inflammatory affect, it effectively promotes mucin production. These actions have been shown to have inhibitory effects in an experimental model of gastritis[36], to cause inhibition of inflammatory cell infiltration of gastric mucosa[37], and to inhibit an inflammatory cytokine (interleukin 8) in the gastric mucosa[38]. With respect to the ocular surface, although there have been reports on the effect of tumor necrosis factor alpha in restoring impaired corneal cell barrier function[39,40], no studies have directly shown that rebamipide exhibits anti-inflammatory effects. Inflammation clearly plays a role in the symptoms of dry eye. The effect of rebamipide in improving symptoms may be attributable to the improvement in tear film stability that is the result of increased mucin levels and to its anti-inflammatory effect. Further studies are warranted on the anti-inflammatory effects of rebamipide in the treatment of dry eye.

In conclusion, this study has demonstrated that the administration of 2% rebamipide by ocular instillation 4 times daily for 4 weeks improves the signs and symptoms of dry eye. These results suggest that rebamipide can successfully improve damaged keratoconjunctival epithelial cells, tear film stability, and quality of life.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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