Medical Treatment for Dry Eye in Japan

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Dry eye is one of the most common diseases observed clinically, affecting 5% to 30% of the global population.¹,² In Japan, sodium hyaluronate ophthalmic solutions have been used to treat dry eye in combination with preservative-free artificial ophthalmic solutions for many years. Based on the concept that tear instability causes dry eye, cyclosporine A ophthalmic solution is not approved for the treatment of dry eye in Japan.

Two new topical eye drops have become commercially available for treating dry eye in Japan. The first is 3% diquafosol ophthalmic solution (Diquas, ophthalmic solution 3%; Santen Pharmaceutical Co., Ltd, Osaka, Japan), commercially available since 2010, which stimulates aqueous and mucous secretion directly on the ocular surface. The other is 2% rebamipide ophthalmic suspension (Mucosta ophthalmic suspension UD2%; Otsuka Pharmaceutical Co., Ltd, Tokyo, Japan), commercially available since 2012, which stimulates mucous secretion. These new eye drops target the tear film layer and increase its stability, facilitating ocular surface-based diagnosis and treatment of dry eye. A recent report has clearly shown that diquafosol and rebamipide are now important treatment modalities for dry eye in Japan.³

In 2015, the Dry Eye Society of Japan proposed tear film oriented diagnosis (TFOD) based on the tear breakup pattern and tear film oriented treatment (TFOT) as an effective therapeutic approach to treating dry eye.⁴ Based on TFOD and TFOT, we expect that each layer of the ocular surface may be targeted by a selective topical therapy, thereby further stabilizing the tear film.⁴

This article focuses on diquafosol solution and rebamipide ophthalmic suspension and describes their use in treating dry eye in Japan.

DIQUAFOSOL

Diquafosol ophthalmic solution (3%) became available in December 2010. The drug is an antagonist of the P2Y2 receptor, which is widely distributed throughout the body. In the eye, the receptor is expressed in the corneal and conjunctival epithelium, including goblet cells and Meibomian glands.⁵ Through the P2Y2 receptor, diquafosol facilitates fluid transport from the serosal to the mucosal side via chloride channel activation following elevation of the calcium ion concentration in epithelial cells on the ocular surface.⁶ In addition, diquafosol sodium increases tear volume and stimulates mucin secretion by secretary goblet cells,⁷,⁸ as previously observed in animal models.⁹–¹³ However, diquafosol does not directly act on the lacrimal glands or stimulate protein secretion.¹⁴ Moreover, diquafosol upregulates the expression of membrane-binding mucin genes in corneal epithelial cells.¹⁵ These actions probably promote tear stability on the side of tear film and in the ocular surface epithelium.¹⁶–¹⁸

Randomized, double-blind, multicenter clinical trials revealed that the diquafosol solution significantly decreases fluorescein corneal and rose Bengal scores compared with artificial tears.¹⁸ In addition, 3% diquafosol significantly decreased rose Bengal scores versus 0.1% hyaluronate ophthalmic solution at week 4. Similarly, diquafosol improved tear film breakup times. Another report suggested the superior efficacy and safety of the 3% diquafosol ophthalmic solution compared with the 0.1% hyaluronate ophthalmic solution.¹⁹ Regarding the long-term efficacy of diquafosol ophthalmic solution (6 months), the therapy was demonstrated to significantly improve both subjective (dry eye symptom score) and objective symptoms (ocular staining score and tear function tests).²⁰ These effects were also observed in patients with mild-to-moderate Sjögren’s syndrome.²¹

Meanwhile, the long-term use of diquafosol to treat dry eye is associated with reductions in ocular higher-order aberrations (HOAs), as well as improvements in tear film stability and corneal epithelial damage.²²

Generally, six times daily administration of 3% diquafosol ophthalmic solution is effective regardless of the severity of dry eye, as 76% of patients experienced improvement in one study.²²

ADDITIVE EFFECT

In addition to monotherapy, an additive effect of the 3% diquafosol ophthalmic solution in combination with 0.1%...
sodium hyaluronate ophthalmic solution has been reported in patients in whom sodium hyaluronate monotherapy was ineffective in terms of objective signs, such as the tear film breakup time and ocular staining scores as well as subjective signs, such as dry eye sensation, pain, and foreign body sensation. Similarly, an additive effect of 3% diquafosol ophthalmic solution plus 0.1% sodium hyaluronate was also reported in South Korea.24

TREATMENT FOR SHORT TEAR BREAKUP TIME–TYPE DRY EYE

Clinically, the short tear film breakup time–type dry eye has been reported to be associated with a shorter tear film breakup time and dry eye symptoms without ocular surface damage and tear deficiency.25,26 The efficacy of the 3% diquafosol solution in short tear film breakup time–type dry eye has been reported in a few studies.27–29 In an exploratory nonrandomized study, the 3% diquafosol solution showed significant improvements in subjective symptoms and tear breakup time at both 1 and 3 months after treatment.25 Another nonrandomized study showed that the use of the 3% diquafosol solution results in significant improvements in visual acuity. However, the 3% diquafosol solution significantly increased the tear breakup time in the symptom-negative group but not in the symptom-positive group.30 A recent report has shown that 3% diquafosol solution generates improvements not only in tear film breakup time but also in intraocular scattering in the short term.27

TREATMENT FOR DRY EYE AFTER LASIK

Treatment with 3% diquafosol ophthalmic solution and 0.3% sodium hyaluronate in patients with dry eye 1 month after LASIK was linked to significant improvements in distance and functional visual acuity.30,31 Longer-term treatment with 3% diquafosol ophthalmic solution for persistent dry eye after LASIK resulted in improvements in subjective symptoms, such as fatigue, dryness, grittiness, discomfort, reading difficulty, and discomfort, although best-corrected visual acuity and tear secretion did not change.24,25 These reports indicated that 3% diquafosol ophthalmic solution would be more effective than conventional therapy using artificial tears or sodium hyaluronate.24,25

TREATMENT FOR CONTACT LENS-RELATED DRY EYE

The diquafosol solution displayed effectiveness in contact lens users, including remarkable increases in tear meniscus height.32–34 After the instillation of the 3% diquafosol ophthalmic solution, tear meniscus height was significantly increased at 5, 15, 30, and 60 minutes versus the baseline values, and the values were significantly greater than those for saline instillation at 15, 30, and 60 minutes. Based on these data, diquafosol would be expected to improve both subjective and objective signs in patients with contact lens-related dry eye.

SAFETY OF DIQUAFOSOL

The most common adverse effects of 3% diquafosol are eye irritation (6.7%) and eye discharge (4.7%), and the majority of these reactions are of mild severity. Meanwhile, no serious treatment-related adverse events have been reported.17,18 Similarly, a multicenter clinical study of “real-world” dry eyes45 identified adverse reactions in 6.3% of patients, and the major adverse reactions were eye discharge, eye irritation, and eye pain. The eye discharge appears to be composed of mucin substances, and, in a sense, its appearance may provide evidence that 3% diquafosol ophthalmic solution stimulates goblet cells. In fact, secretory mucin levels in tear fluid were boosted by 3% diquafosol ophthalmic solution treatment.13 Moreover, 52% of cases of eye irritation and eye pain occurred on the day of the first instillation, and 79% of the cases were resolved within 28 days.58 These reports collectively support the safety of diquafosol eye drops.

REBAMIPIDE

Rebamipide is a quinolinone derivative with mucin secretagogue activity.37–39 Based on reports that rebamipide suspension increases the number of periodic acid–Schiff-positive cells in rabbit eyes,40,41 the therapy was expected to be effective in the treatment of dry eye.

PHARMACOLOGICAL EFFECT OF REBAMIPIDE

The pharmacologic mechanism of rebamipide has been clarified. Although whether rebamipide induces MUC1 and MUC4 remains controversial,42–44 the drug has been demonstrated to increase MUC16 biosynthesis.59 In this report, rebamipide had no effect on the expression levels of Notch intracellular domains, suggesting that its effects on MUC16 biosynthesis are regulated by the differential upregulation of MUC16 in human corneal epithelial cells opposed to Notch signaling.44 Meanwhile, rebamipide instillation has been reported to accelerate the recovery of tight junctions47,48 and microvilli.49 Increased numbers of goblet cells were observed after more than 2 weeks of rebamipide instillation.49 These effects may be mediated by the induction of epithelial differentiation. Therefore, although rebamipide was initially recognized as a mucin secretagogue, the drug is also currently recognized as an activator of epithelial differentiation. More over, rebamipide increases tear stability by activating epithelial differentiation as opposed to increasing the tear volume. Based on its superior mucin secretagogue activity,55 diquafosol improves tear film stability by boosting the tear volume and mucin secretion, whereas rebamipide improves the epithelial condition.

CLINICAL EFFECT OF REBAMIPIDE IN TREATING DRY EYE

Clinically, a 2% rebamipide suspension has been reported to improve fluorescein corneal scores.50–54 In addition to objective symptoms, a rebamipide suspension can significantly improve subjective symptoms, such as foreign body sensation, dryness, photophobia, eye pain, and blurred vision as well as patients’ overall impressions.50,53,55 Rebamipide was significantly more effective against objective and subjective symptoms than 0.1% sodium hyaluronate in the treatment of dry eye. Rebamipide is reportedly effective in patients with Sjögren’s syndrome with or without punctal occlusions53 and patients with dry eye undergoing corneal refractive surgery concerning both ocular parameters and optical quality.55 Rebamipide has also been reported to alleviate objective and subjective symptoms in patients with dry eye who wear contact lenses.16

Regarding HOAs, a rebamipide suspension can improve optical quality in patients with typical dry eye57 and those with the short breakup time of dry eye.58
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Rebamipide suspension is undissolved and packaged in a dropperette. It is also preservative free, making it advantageous for treating dry eye.

Rebamipide exerted anti-inflammatory effects and promoted epithelial wound healing in animal models. Therefore, rebamipide is expected to clinically suppress inflammation. However, an apparent clinical effect has not been identified regarding this issue, and further investigation is required.

The most common adverse effects of a 2% rebamipide suspension were dysgeusia (9.7%) and eye pruritus (4.3%), both being of mild severity.

Recently, dacyrocystitis accompanied by white masses in the canaliculus and lacrimal sac was observed following treatment with the drug in several cases. (unpublished data). The frequency of this event has not been clarified, although it is expected to be as low as 0.1% to 0.01%; however, further investigation is warranted.

AREAS FOR FUTURE INVESTIGATION

The diquafosol solution and rebamipide suspension are effective in improving both objective and subjective signs of dry eye. Tear film and Ocular Surface Society, Dry Eye Workshop II (TFOS DEWII) has introduced the efficacy of these two eye drops as mucin secretagogues. However, which therapy is more effective clinically has not been clarified, although there are a few reports that have determined the eye drop that is effective clinically for specific types of dry eye.

For example, 3% diquafosol has been shown to be effective for patients with dry eye with chronic graft versus host disease, although a long-term follow-up of patients receiving 3% diquafosol solution has not shown significantly improved tear film volume. In contrast, both diquafosol and rebamipide are compatible for treating dry eye in office workers. Further investigation regarding their effects in the treatment of different types of dry eye is needed.

Despite their effectiveness, the treatments for severe dry eye associated with causes of aqueous tear deficiency, such as Sjögren’s syndrome, are limited. Although diquafosol can increase tear volume, more effective eye drops that can remarkably increase tear volume are needed. Meanwhile, rebamipide exerted anti-inflammatory effects in animal models, and the therapy is expected to have some benefit in the treatment of severe aqueous deficiency; however, no study has reported these effects. As the pharmacologic mechanism of rebamipide has not been clarified, investigation of its pharmacuetic properties would be helpful for improving the treatment of dry eye. As previously noted, diquafosol mainly improves tear film stability by increasing tear volume and mucin secretion, whereas rebamipide improves the epithelial condition. However, both therapies upregulate MUC16, thus increasing tear stability. Further investigation of the use of these two eye drops for the highest clinical impact is necessary.

The etiology of dry eye is still controversial, and resolution of this problem requires further investigation.

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