Review of: "Recent Trends in Dry Eye Disease Treatment in Asia"

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Potential competing interests: No potential competing interests to declare.

Purpose of review. Summarize recent trends in the treatment of dry eye disease (DED) in Asia.

Recent findings. In recent years, effective new generation eye drops, such as dicuafosol ophthalmic solution and rebamipide ophthalmic solution, which are mucin secretion stimulants, and cyclosporine ophthalmic solution, an immunosuppressive agent, have been approved in various countries for the treatment of DED. Additional newer adjunctive therapies such as laser acupuncture as an adjunctive therapy when eye drops do not provide satisfactory results, new generation intense pulsed light therapy for meibomian gland dysfunction-related DED, and human umbilical cord serum eye drops for severe DED are also of interest. These adjunctive therapies target the suppression of inflammation primarily.

Summary. New generation eye drops have made it possible to control mild DED. For patients with moderate to severe disease, the addition of eye drops and adjunctive treatment is recommended. Because DED with an unstable tear film is common in Asia, treatment of DED in Asia might first include mucin secretion-promoting eye drops, with anti-inflammatory treatment preferred if additional treatment is needed. In addition, further research is needed to improve treatment continuity because DED is a chronic disease requiring continuous treatment.

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1. Introduction

The first choice for dry eye disease (DED) treatment is treatment with artificial tear supplements. Until now, it has been the primary treatment for DED, but because they have a short retention time on the ocular surface, its efficacy is limited to only temporary improvement of signs and symptoms.. Corticosteroid eye drops although reduce inflammation and improve the symptoms of DED, the long term usage leads to glaucoma and cataract. No evidence has been established that nonsteroidal anti-inflammatory drug eye drops are effective for tear film stability, and there is concern about the side

effect of decreased corneal perception. Therefore, sodium hyaluronate ophthalmic solution, which improves subjective symptoms and corneal damage, and does not cause serious adverse events, became widely used. Sodium hyaluronate binds to fibronectin and improves corneal conjunctival epithelial disorders by promoting epithelial cell adhesion and extension through its action [1][2], and also exhibits water retention properties by retaining water molecules within its molecules [3]. However, the effect on tear film stability was minor, and in a few cases, there was no improvement in subjective symptoms or objective findings.

In Asia, the short tear film breakup time-type DED, accompanied by tear film instability, is common[4]. The Asia Dry Eye Society has established the following diagnostic criteria for dry eye in Asia: Dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage [5]. This indicates the importance of tear film stability in the treatment of DED. New generation of eye drops and new adjunctive therapies to enhance tear film stability have been reported. The purpose of this study is to evaluate recent eye drops and adjunctive therapies for the treatment of DED in Asia.

2. Major Therapy (New Generation Eye Drops)

Table 1 summarizes the new generation eye drops for DED treatment in Asia.

Generic name	Main pharmacological action	Recommended frequency of instillation per day	Brand name
Diquafosol	Mucin secretion promotion	6 3*	Diquas Diquas LX*
Rebamipide	Mucin secretion promotion	4	Mucosta
Cyclosporine	Immune suppression	1	Ikervis

Table 1. New generation eye drops for DED treatment in Asia

*Long-acting diquafosol

2.1. Diquafosol

Diquafosol is a dinucleotide derivative that acts on the $P2Y_2$ receptor [6]. $P2Y_2$ receptors are expressed in the conjunctival epithelium, corneal epithelium, lacrimal gland secretory epithelium, accessory lacrimal gland secretory epithelium, and meibomian gland secretory epithelium [7]. Activation of $P2Y_2$ receptors promotes mucin and water secretion on the ocular surface via Ca^{2+} and Cl^- channels [8][9][10][11][12] and thickens the lipid layer in the tear fluid[13][14]. Lacrimal fluid secretion

was found to increase for 5 to 30 minutes after instillation [10], and this increase is not related to lacrimal gland function [15]. The fact [10] that the duration of lachrymal fluid increase with artificial tears is only 5 minutes after instillation also supports the lachrymal volume-increasing effect of diquafosol. Diquafosol has also been reported to increase the tear film lipid layer for up to 60 minutes [16]. Diquafosol stabilizes tear fluid by increasing tear fluid volume and increasing mucin and lipids in the tear fluid. On the other hand, diquafosol is thought to promote epithelial cell proliferation and repair by promoting the phosphorylation of epidermal growth factor receptors and extracellular signal-regulated kinases [17]. In fact, dicuafosol has been shown to reverse the apoptosis of corneal epithelial cells [18]. In a multicenter clinical trial [19], diquafosol ophthalmic solution improved tear secretion and corneal epithelial barrier function and significantly reduced corneal epithelial damage. This study showed that it was effective not only for the short tear film breakup time-type DED, but also for the tear fluid deficiency-type DED [19]. Diquafosol ophthalmic solution has also been reported to improve not only subjective symptoms of DED (dryness, foreign body sensation, eye pain, photophobia, and blurred vision), but also practical vision [20]. Thus, although diquafosol ophthalmic solution is a new generation of eyedrops useful in the treatment of DED, the frequent administration, six times a day, has hindered the continuity of treatment [21]. Therefore, the long-acting dicuafosol ophthalmic solution was developed, and approved in Japan in 2022. In this ophthalmic solution, polyvinylpyrrolidone is added to the conventional diquafosol ophthalmic solution to prolong the effect of the ophthalmic solution [22]. The recommended administration is three times a day, and the efficacy and safety of this ophthalmic solution have been shown to be equivalent to those of conventional ophthalmic solutions [22]. Further clinical trials are expected to be conducted.

2.2. Rebamipide

Rebamipide, which is a quinolinone derivative, has been approved and widely used for the treatment of gastritis and gastric ulcers through its mechanism of increasing mucin in the gastric mucosa. Focusing on this mucin-increasing effect, it was studied in an animal model of ocular mucin depletion and reported that rebamipide increased the number of mucin-producing conjunctival goblet cells, increased corneal and conjunctival mucin, and improved corneal conjunctival epithelial damage [23]. When human corneal epithelial cells were cultured with rebamipide, it was observed that mucin-like glycoproteins were produced and MUC1, MUC4, and MUC16 were expressed [24][25]. Furthermore, in corneal epithelial wounding models, the epithelium also promotes microvillus recovery during epithelial repair, leading to early restoration of tight junctions between epithelial cells [26]. These results indicate that rebamipide ophthalmic solution improves tear film stability and ocular surface conditions by secreting mucin-like substances [27]. In fact, long-term administration of rebamipide has been reported to increase the stability of the tear film on the cornea and improve corneal epithelial damage [28]. Topical therapy also improves subjective symptoms of DED[28]. Rebamipide ophthalmic solution is effective in the treatment of DED, and its mechanism of action suggests that it may be particularly effective in patients with keratoconjunctival epithelial damage. Therefore, it is also recommended for the treatment of perioperative DED in ophthalmic surgery [29].

2.3. Cyclosporine

Inflammation is one of the causes of DED and also one of the pathologies caused by DED[5][30]. Animal studies have confirmed that dry stress induces the release of Th1-type cytokines on the ocular surface and disrupts the corneal epithelial barrier associated with Th-17 cells [31][32]. Proinflammatory cytokines are increased in the tear fluid of DED patients [33], and inflammation decreases mucin production and secretion in the corneal conjunctival epithelium[34][35], destabilizing the tear film. Therefore, it is necessary to control inflammation and improve the unstable tear film. Cyclosporine ophthalmic solution, an immunosuppressive agent used to control inflammation, is known to be an effective treatment for DED [36]. Normal tear fluid contains anti-inflammatory factors such as TGF-β secreted by the lacrimal gland and conjunctival goblet cells, and cyclosporin increases TGF-β levels [37]. Cyclosporine also decreases lymphocyte infiltration in the lacrimal glands and conjunctival tissue and inhibits the expression of inflammatory factors [38]. Treatment of patients with mild DED with cyclosporin has been shown to reduce tissue damage due to inflammation [39]. In addition, the greatest advantage of the new generation cyclosporine ophthalmic solution is that it is effective with only one instillation per day. Also, it was reported that there were no findings to suggest the systemic absorption of ciclosporin after instillation [40]. In view of the above, the new generation ciclosporin ophthalmic solution is an effective option for the treatment of DED. However, inflammation in the short tear film breakup time-type DED, which is more common in Asia, is not considered to be the core of DED treatment in Asia because it is a secondary pathology [5]. Therefore, it has been suggested that cyclosporin should not be administered alone, but that in combination with a mucin secretagogue it can be an effective treatment method [41].

3. Adjunctive Therapy

Currently, the primary adjunctive therapy for DED is punctal occlusion. The goal of treatment is to occlude the patient's lacrimal duct, allowing tear fluid to accumulate on the ocular surface. While this treatment improves tear film stability [42] [43] and thus is a useful adjunctive therapy, the side effects of plug discomfort and lacrimation are unavoidable[43][44][45]. Newer adjunctive therapies are therefore attracting attention.

3.1. Laser Acupuncture

Acupuncture has been reported to be effective in the treatment of DED[46][47]. Acupuncture modulates the autonomic and immune systems by dilating blood vessels and increasing neuropeptides [48], which in turn regulate the autonomic nervous system and immune system [49][50][51]. In DED treatment, the instability of the tear film is improved by increasing tear protein secretion, modulating hormone levels and lacrimal gland metabolism, increasing the acetylcholine content of the lacrimal gland, modulating vasoactive intestinal peptides, and reducing inflammatory cytokines on the ocular surface [52] [53]. Laser acupuncture combines the pathway and acupuncture point theory of Chinese medicine with modern laser technology. This technology is short, painless, sterile, and noninvasive because it uses low-intensity, nonthermal laser irradiation to stimulate acupuncture points rather than metal needles [54][55]. The complications of conventional needle acupuncture (fainting, folding, bending, and stuck needles) are also avoided. Therefore, from the viewpoints of efficacy and safety, laser acupuncture has been suggested to be a useful complementary therapy when eye drop therapy is

inadequate [52].

3.2. Intense Pulsed Light

Intense pulsed light therapy was initially used in the cosmetics industry and for dermatological conditions (hypertrichosis, benign cavernous hemangiomas, venous malformations, telangiectasias, pigmented lesions, etc.) [56][57][58][59]. Intense pulsed light devices provide selective heat delivery to specific structures with xenon flashlamps that emit intense multicolor light ranging from the visible to infrared spectrum by adjusting wavelength, penetration depth, and target site [60][61]. The improvement in DED when patients with facial rosacea underwent intense pulsed light therapy suggested that it might be applicable to the treatment of meibomian gland dysfunction [62], and subsequent studies have confirmed that intense pulsed light therapy is an effective treatment for DED associated with meibomian gland dysfunction [63][64][65][66][67][68][69]. Light energy from the intense pulsed light is absorbed by chromophores and converted to thermal energy, which coagulates superficial blood vessels and eliminates the lid margin telangiectasia, thereby reducing ocular surface inflammation [70]. These responses have been shown to reduce inflammatory markers in the tear fluid of patients with meibomian gland dysfunction-related DED [65]. In these regards, intense pulsed light therapy is a useful adjunctive therapy for meibomian gland dysfunction-related DED. However, conventional intense pulsed light devices offer few variations in energetic and pulse intensity, making it difficult to treat meibomian gland dysfunction according to its severity. The new-generation intense pulsed light devices have been improved, eliminating these shortcomings and increasing efficacy and safety [71].

3.3. Human Umbilical Cord Serum Eye Drops

Autologous serum ophthalmic solutions have been reported to be effective in the treatment of severe dry eye, recurrent corneal erosion, graft-versus-host disease, and so on [72][73][74][75][76]. Autologous serum contains growth factors such as epidermal growth factor, acidic and basic fibroblast growth factor, platelet-derived growth factor, hepatocyte growth factor, vitamin A, transforming growth factor, substance P, insulin growth factor, nerve growth factor, fibronectin and serum anti-protein enzyme [77]. These growth factors ameliorate corneal epithelial damage by promoting proliferation, differentiation, and maturation of the surface epithelium. They also cause anti-inflammatory effects. Human umbilical cord serum is thought to have a more potent therapeutic effect than autologous serum due to its higher concentration of growth factors, and is applicable to Stevens-Johnson syndrome and ocular chemical injury, in addition to the aforementioned diseases that benefit from autologous serum ophthalmic solutions [77][78][79][80][81][82][83][84]. However, there are reports [85][86] that corneal epithelial damage was not significantly improved by autologous serum eye drops, so there may be a question mark over their ability to improve epithelial damage. In light of the above, human umbilical cord serum appears to be a safe and effective adjunct in severe DED, primarily due to its potent anti-inflammatory properties.

4. Conclusions

Reports indicate that new generation DED therapies are more effective than artificial tears and sodium hyaluronate, and

that mild DED is now controllable. In Asia, where the short tear film breakup time-type DED is more common, the goal of treatment is to stabilize the tear film, so the first option is to administer mucin-secreting ophthalmic solutions. Although there is some controversy over the use of dicuafosol versus rebamipide, the mechanism of action suggests that dicuafosol may be better for DED, which is primarily a tear disorder, and rebamipide for DED, which is primarily an epithelial disorder. Moderate to severe DED that cannot be controlled with mucin secretagogues is preferably addressed by the addition of anti-inflammatory therapy. Cyclosporine ophthalmic solution and the adjunctive therapies presented in this study are recommended.

Because DED is a chronic disease, an important issue for future DED treatment is improving treatment adherence. It has been reported that only about 10% of DED patients are on instillation as often as recommended in the package insert [21]. A long-acting formulation of dicuafosol has been developed, and future results are expected to show whether it improves adherence. Further studies are also needed to achieve good adherence.