• APAO 2015 • Lunch Symposia •

Improving the QOL of dry eye patients and prospects for the future

• DATE • April 2, 2015

• VENUE • Yuexiu Hall,
Guangzhou Baiyun International Convention Center

Chair

Zuguo Liu

Xiamen Eye Centre of Xiamen University, China

Speaker 1

Louis Tong

Singapore National Eye Centre Corneal and External Eye Disease Service, Singapore

Speaker 2

Shizuka Koh

Osaka University Graduate School of Medicine, Japan

Speaker 3

Xiaoming Yan

Eye Center, First Hospital Peking University, China

Incidence of dry eye

Dr. Louis Tong
Singapore National Eye Centre Corneal and External Eye Disease Service, Singapore

Dry eye is a multi-factorial disorder of the preocular tear film that reduces visual-function-related quality of life, and has a high prevalence in Asia.

The United States Beaver Dam study demonstrated an incidence of adult dry eye of 13.3% (95% confidence interval [CI] 12.0–14.7%) over 5 years, and showed that dry eye was associated with age (p<0.001);[1] however, the incidence of dry eye in Asia has not been reported.

This presentation reports the findings of a population-based cross-sectional study (and then those of a cohort study with follow-up) that aimed to investigate the 5-year incidence of symptomatic tear dysfunction in adult Malays aged 40–79 years in Singapore, and to identify potential factors associated with dry eye incidence. Overall 16,069 cases were stratified into four age groups of 1,400 cases each; 74.4% were eligible, and the response rate was 78.7%, for a final sample size of 3,280 (*Figure 1*).

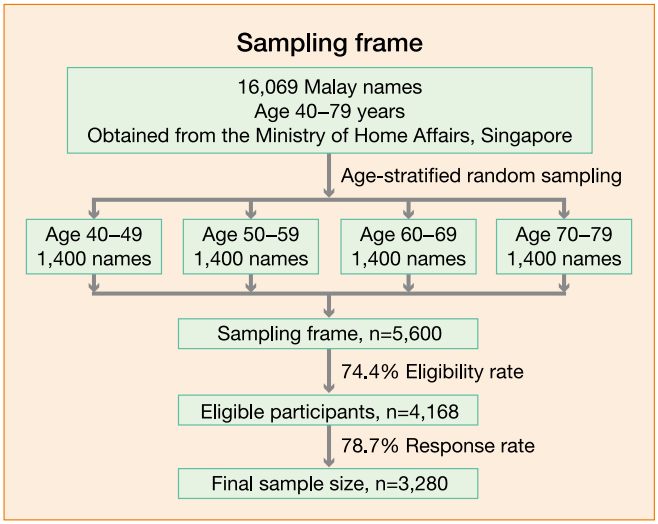


Figure 1. Study flow chart.

Examinations at the clinical trial center included a questionnaire, various blood tests including HbA1c, glucose and lipids, and an ophthalmic evaluation (photographs, vision check, glaucoma studies).

Answers to six questions from the original Salisbury Eye Evaluation Study[2] focusing on dry eye or symptoms related to tear dysfunction and symptom frequency were collected. Of the 1,901 cases successfully reexamined at 5-year follow-up (644 were deemed ineligible, and 735 were not examined), 1,687 were considered at risk for dry eye. Of these, 86 developed dry eye at a follow-up visit and 1,596 had no dry eye.

At the second visit, participants had lower incidences of hypertension, cardiovascular disease history, and diabetes mellitus than did non-participants. The 5-year incidence of dry eye was 5.11% (95% CI 5.0–7.4%) (*Table 1*); however, none of the following putative risk factors were significantly associated with the incidence of dry eye: age, sex, income, current smoker, history of thyroid disease, body mass index, systolic blood pressure, anti-hypertensive medication, intraocular pressure and cup-to-disc ratio. There was a borderline significance for the association between increased risk of dry eye and lower diastolic pressure (p=0.05).

Table 1. Five-year incidence rate of dry eye in Malays living in Singapore.

	Incidence		P-value
	Total No.	(%)	
Total	1,682	5.11	
Age-specific incidence			
40–49	476	5.46	0.97
50–59	595	4.54	
60–69	381	5.51	
>70	230	5.22	

In summary, the incidence was approximately 1% annually, which was lower than that reported in the Beaver Dam study. This might be explained by the use of a different definition of dry eye in the Beaver Dam study, which asked one question regarding dry eye compared with six in the current study.

A false low incidence in the Singapore Malay eye study might be explained by a reduced number of observed cases because of a high rate of non-examined cases and deaths within the group. This is in accord with results of other studies showing that high morbidity and mortality are associated with dry eye. In contrast to the Beaver Dam study, we did not observe an effect of age on the incidence of dry eye.

Study strengths included the large sample size, unbiased selection, and comprehensive evaluation. Limitations included a lack of corneal staining, Schirmer's test, and examination of tear break-up times, tear osmolarity or tear cytokines, as well as the fact that allergic eye disease cases were not excluded.

In conclusion, the 5-year incidence of dry eye among adult Malays in Singapore is 5.1% with no association with age or sex. Future studies will investigate Singapore Indians and Chinese.

[1] Moss SE, et al. *Arch Ophthalmol.* 2004;122:369–73.
[2] Muñoz B, et al. *Arch Ophthalmol.* 2000;118:819–25.

Impact of dry eye disease on quality of vision

Dr. Shizuka Koh
Osaka University Graduate School of Medicine, Japan

Tear film is important for maintaining a healthy cornea and conjunctiva. In healthy eyes, a smooth tear film is formed by blinking to create a clear optical surface; however, when the tear film breaks up or exposes the rough corneal surface, an irregular optical surface may compromise visual function. The recent definition of dry eye in the 2007 Dry Eye Workshop (DEWS) report[1] states that "dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."

Dry eye rarely affects visual function, except in advanced cases. A wavefront sensor is used to evaluate optical quality quantitatively (Hartmann images and color-coded maps) by measuring high-order aberrations undetected by conventional visual acuity tests.

Using a wavefront sensor, we previously measured higher-order aberrations (HOAs) before and after tear film break-up to investigate the effect of tear film break-up on optical quality.[2] Measurements after blinking indicated a regular spotted pattern and no difference in the color-coded map; however, after tear film breaks, a distorted spot pattern and changes in the color-coded map were observed, indicating significantly increased HOAs and decreased optical quality.

To investigate dynamic changes in optical quality due to tear film break-up, HOAs were measured every second for 10 seconds between blinks. In a normal eye, simulated retinal images were stable and the retinal image quality was good throughout between blinks. However, in a case of short BUT-type dry eye which is characterized by decreased tear film stability, the optical quality degraded as the tear film became more unstable.

For a case of aqueous-deficient dry eye, decreased tear volume and decreased tear stability with corneal staining in the optical zone was observed. The measurement of HOAs demonstrated a distorted retinal image from just after the blink that continued between blinks.

Because decreased tear film stability is a major etiological mechanism underlying dry eye in Japan, new dry eye treatments aim to improve tear film stability. A new treatment concept, tear film oriented therapy (TFOT) (*Figure 1*), includes two new topical pharmacological agents: i) 3% diquafosol ophthalmic solution (Diquas® from Santen approved in 2010 for use in Japan and South Korea), a P2Y2 receptor agonist that activates P2Y2 receptors on the ocular surface to stimulate mucin secretion and tear fluid secretion that stabilizes the tear film; and ii) 2% rebamipide ophthalmic suspension (Mucosta UD 2%® from Otsuka), which stimulates mucin secretion. Recently, the Dry Eye Society of Japan advocated TFOT as an effective therapeutic approach to dry eye. Based on TFOT, we expect that each layer of the ocular surface can be targeted by selective topical therapy, thereby stabilizing the tear film.

Next, I will describe highlights of some of our studies evaluating the clinical efficacy of diquafosol in aqueous tear-deficient dry eye patients.

First, we evaluated the clinical efficacy of 4 weeks of treatment with diquafosol in patients with aqueous-deficient dry eye. After the 4-week treatment, dry eye symptoms were significantly decreased, and corneal staining scores and BUT were significantly improved (all $p<0.001$).[4]

We reported a representative case of a 61-year-old woman with aqueous-deficient dry eye and Sjögren's syndrome. *Figure 2* shows the image of her corneal ocular surface, the color-coded map of HOAs and simulated retinal images. The blurred retinal image is indicated by the simulated retinal

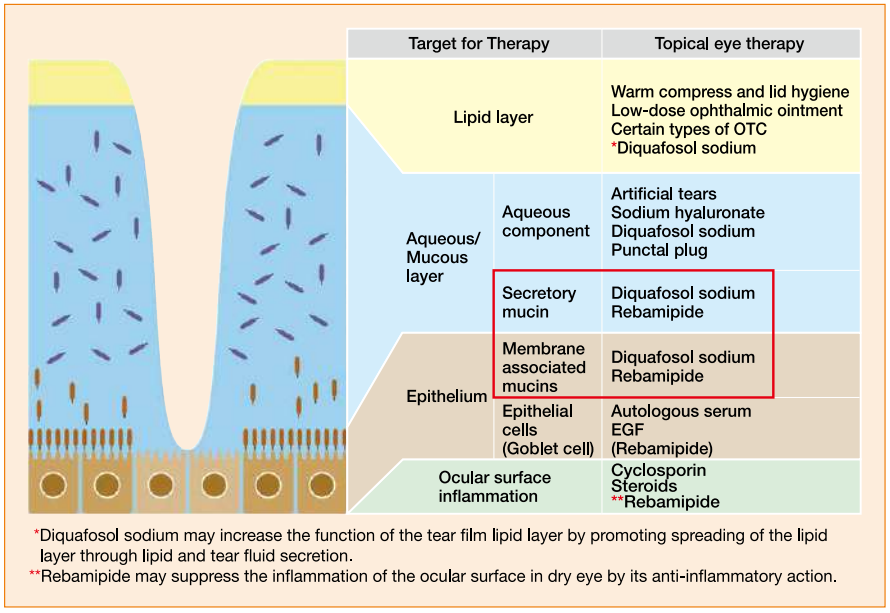


Figure 1. Tear film oriented therapy.[3]

image (Landolt C).[4]

At the baseline visit, one eye drop of diquafosol was administered and we measured HOAs at 15 minutes after the instillation. However, there was no significant change, and the retinal image was still blurred. After 4 weeks of diquafosol treatment, the corneal staining and retinal image quality were improved significantly. Thus, diquafosol that was administered to treat aqueous-deficient dry eye was also effective in improving the optical quality of dry eye.

Numerical data for the efficacy of diquafosol on optical quality are shown in *Figure 3*.[5] The instillation of diquafosol 15 minutes after the baseline showed that short-term treatment with diquafosol was not effective; however, at 4 weeks after baseline, diquafosol significantly decreased HOAs, and improved optical quality compared with the controls.

In another study[5], we investigated the long-term effects of diquafosol. A 60-year-old woman with aqueous-deficient dry eye and Sjögren' s syndrome had been treated with Hyalein® 0.1% (sodium hyaluronate 0.1%), a preservative-free artificial tear ophthalmic solution. However, the patient still complained of dry eye symptoms. Then, treatment was switched from Hyalein® to Diquas®. At 1 month after switching to Diquas® treatment, the corneal staining was markedly improved, and there were also improvements in subjective dry eye symptoms and BUT (*Figure 4*). Clinical efficacy continued for 6 months. To date, this patient has been using Diquas® for more than 4 years and is still in good condition.[5] Optical quality and retinal image quality were greatly enhanced with improved dry eye.

Taken together, these studies indicate that diquafosol can improve tear film stability by inducing the secretion of mucins and tear fluid, which leads to the improvement of dry eye symptoms, ocular surface damage, and optical quality.

Interestingly, the concept of "mucin" treatment is currently a hot topic, and has even been included in beauty magazines in Japan, thus indicating a high level of interest in this treatment.

In summary, dry eye is a chronic disease of the tears and ocular surface resulting in visual disturbances. Diquafosol is a treatment option for dry eye as it improves tear film stability leading to improved ocular symptoms, ocular surface damage, and optical quality.

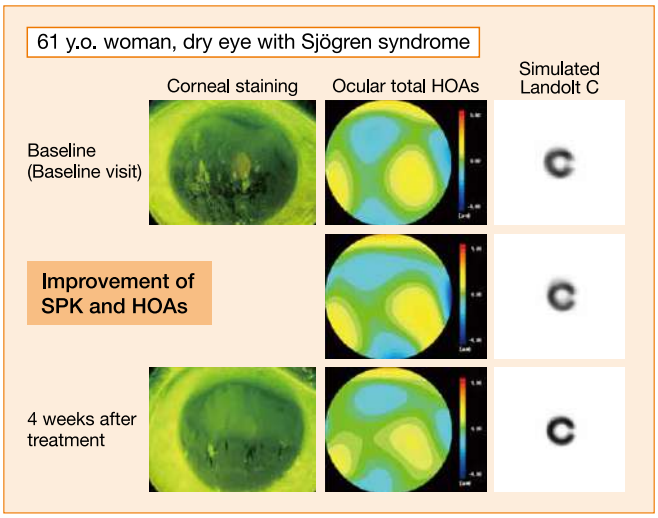


Figure 2. Diquafosol improves optical quality.[4]

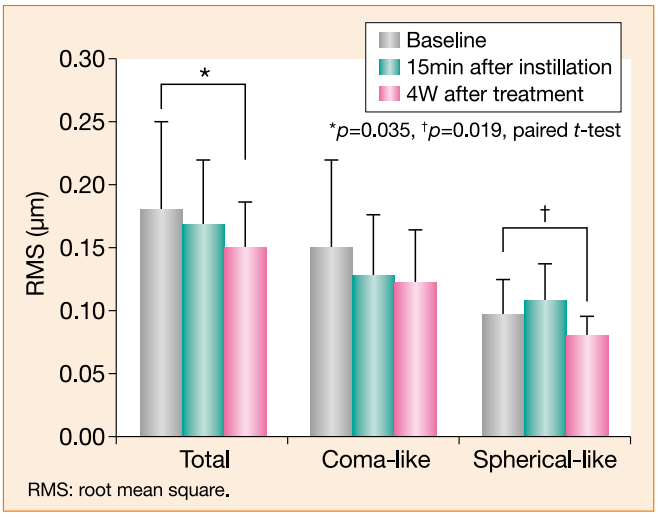


Figure 3. Diquafosol decreases higher-order aberrations.[5]

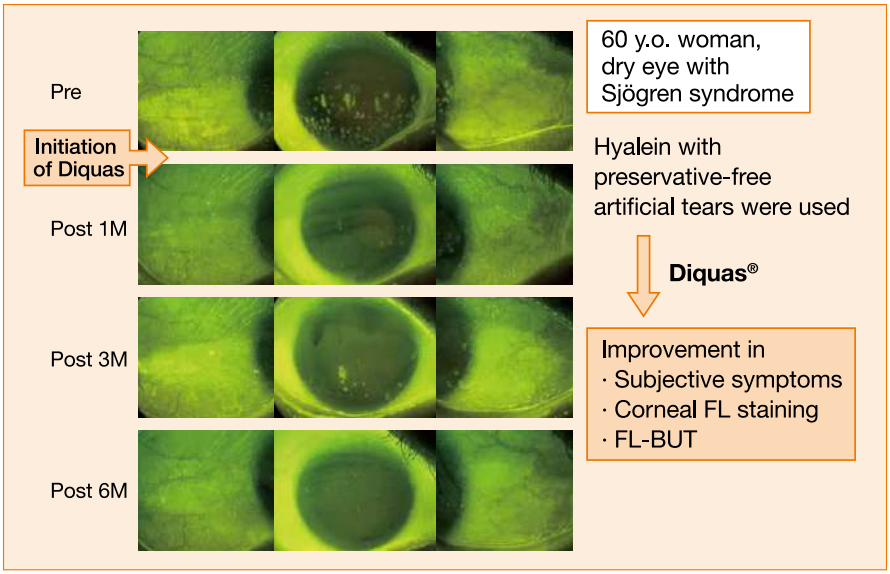


Figure 4. Long term results of diquafosol treatment in a patient with aqueous-deficient dry eye.[5]

[1] Yokoi N, Georgiev GA, Tear-film-oriented diagnosis and therapy for dry eye. Dry Eye Syndrome: Basic and Clinical Perspectives (Yokoi N. ed.), pp96–108, Future Medicine Ltd, London, 2013.
[2] Koh S, et al. *Am J Ophthalmol.* 2002;134:115–7.
[3] Dry Eye Society of Japan http://www.dryeye.ne.jp/en/tfot/index.html
[4] Koh S, et al. *Acta Ophthalmol.* 2014;92:e671–5.
[5] Koh S, et al. *Jpn J Ophthalmol.* 2013;57:440–6.

Tear film-oriented therapy

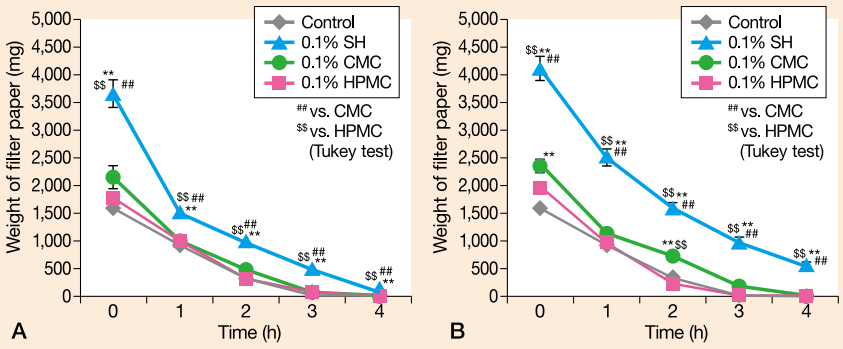
Dr. Xiaoming Yan
Eye Center, First Hospital Peking University, China

Dry eye is a common eye disease that causes a vicious cycle of damage to the tear film and ocular surface epithelium, which normally maintain one another, resulting in tear film instability and damage to the superficial epithelium. Factors that contribute to the development of dry eye include tear film components and corneal epithelium. The most important factors responsible for the maintenance of tear film stability include lipids and mucins. The outer lipid layer retards evaporative tear loss and the inner lipid layer stabilizes the tear film. The mucin family consists of secretory mucins and membrane-associated mucins. An important secretory mucin, MUC5AC, produced by goblet cells, maintains the clean ocular surface, stabilizes the tear film, and retards evaporative tear loss. Membrane-associated mucins produced by epithelial cells of the conjunctiva and cornea form a glycocalyx with the microvilli structure of the ocular surface to protect epithelial cells and provide a hydrated layer.

Current medical therapy for dry eye treatment includes artificial tears, sodium hyaluronate, anti-inflammatory agents, and environmental strategies. However, these therapies do not fully satisfy the requirements of clinical practice; thus, there is a great demand for therapeutic agents with a novel mechanism of action.

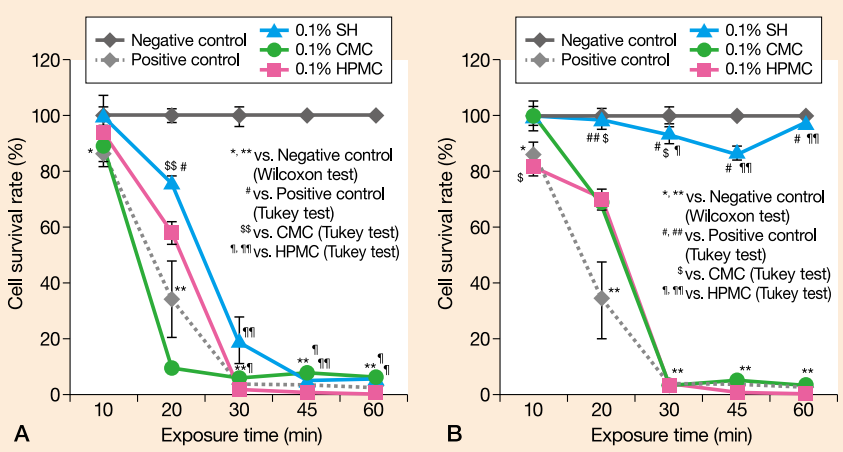
In vitro studies have demonstrated that sodium hyaluronate (0.1 and 0.3% solutions) has a greater water retention ability (***Figure 1***) and protective effect (***Figure 2***) as well as the ability to stimulate corneal epithelial migration and adhesion (synergistic effect with fibronectin), compared with artificial tears (carboxymethylcellulose, and hydroxypropyl methylcellulose).[1] In addition to replenishing water, sodium hyaluronate has been widely used to treat cornea and conjunctiva epithelium disorders. A randomized clinical trial in subjects with superficial corneal abrasions caused by mechanical damage in China demonstrated that 3 days of treatment with sodium hyaluronate eye drops had the same clinical effectiveness rate compared with the control group treated with recombinant bovine basic fibroblast growth factor (86.67% vs 93.33%, respectively) and that patients were cured by day 7.[2]

Cationorm® is a new drug for the treatment of dry eye (***Figure 3***) that consists of a cationic oil-in-water emulsion. These positively charged oil nanodroplets undergo electrostatic interactions with the negatively charged ocular surface and in addition they function as an oil supplement. Cationorm® effectively restores the three layers of the tear film via multiple mechanisms: i) lipid replenishment of the lipid layer with reduced evaporation, increased tear film stabilization, and improved break-up time (BUT); ii) lubrication of the mucin layer with optimal spreading,



Water retention ability of 3 ocular surface lubricants: sodium hyaluronate (SH), carboxymethylcellulose (CMC), and hydroxypropyl methylcellulose (HPMC). Standard filter papers were soaked with 5 mL of each of the lubricants and left in an open container at 25°C and a humidity of 36% to 38%. The weight of the filter papers was measured hourly for 4 hours. Comparisons of 0.1% (A) and 0.3% (B) solutions are shown. The SH-moistened filter papers are significantly heavier at all time points than controls moistened with Milli-Q water in a concentration-dependent manner.

Figure 1. ***In vitro*** **efficacy of ocular surface lubricants against dehydration.**



Protective effect of different ocular surface lubricants, SH, CMC, and HPMC, on HCECs from dehydration. Cells were exposed to the test lubricants for 1 hour and placed under dehydrating conditions. The survival rate of the cells was calculated and compared. The negative controls were cells not dried (100% survival rate), and positive controls were cells pretreated with culture medium only and dried similarly. Comparisons of 0.1% (A) and 0.3% (B) solutions are shown. In a dosedependent manner, SH has a significantly higher protective effect at all times.

Figure 2. Increased protective effect of sodium hyaluronate compared with other ocular surface lubricants.

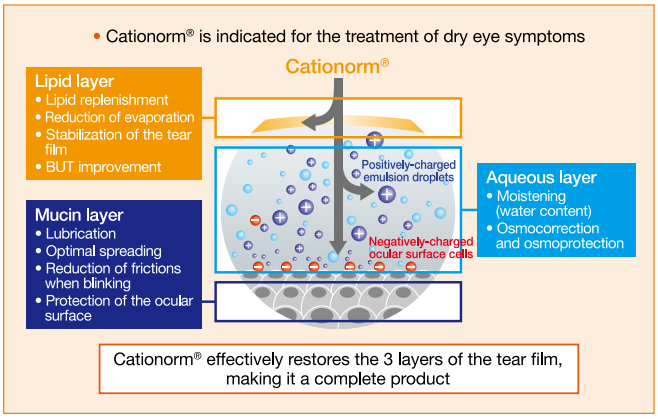


Figure 3. Mechanisms of action of Cationorm® for dry eye.

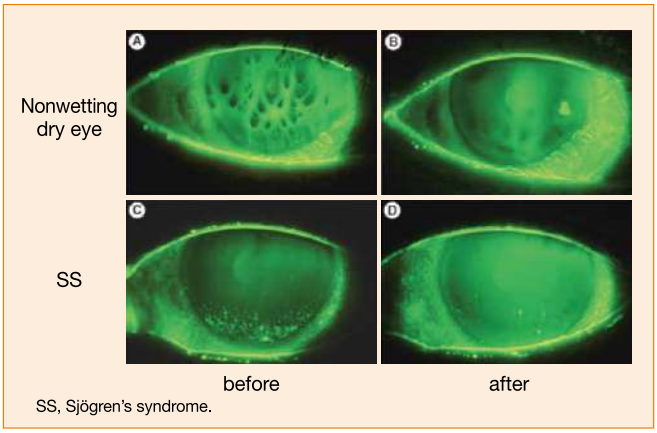


Figure 4. Effect of Diquas® on dry eye.

reduced friction, and increased protection; and iii) enhanced moisture, osmocorrection, and osmoprotection in the aqueous layer. Therefore, it is a complete stand-alone product for the treatment of dry eye.

Recently, new types of solution for dry eye treatment have been introduced in Japan and Korea. These solutions are diquafosol sodium 3% (Diquas®; in clinical use in Japan and Korea since 2010) and rebamipide (Mucosta®; in clinical use in Japan since 2012). Both drugs promote the secretion of water and mucins of the tear film, and increase the expression of membrane-associated mucins in the superficial epithelium. These treatments target and treat each abnormality of the tear film, and collectively are termed tear film-oriented therapy (TFOT).

Diquas® is the world's first P2Y2 receptor agonistic ophthalmic solution and has a novel pharmacological mechanism of action to treat dry eye. The P2Y2 receptor agonist binds to P2Y2 receptors expressed by conjunctiva epithelial membranes and goblet cells to activate calcium-dependent chloride channels and promote water and mucin secretion.

A previous randomized, double-blind, multicenter study of diquafosol sodium 3% in 286 Japanese dry eye patients [3] showed that diquafosol sodium 3% and sodium hyaluronate 0.1% had similar efficacies in terms of improving fluorescein staining scores, although diquafosol sodium 3% had superior efficacy for improving Rose Bengal staining scores as well as a good safety profile (***Figure 4***). Similar efficacy was observed for the same treatment in Chinese and Singaporean dry eye patients (n = 497).[4]

The second new drug for the treatment of dry eye patients, Mucosta®, is a gastroprotective drug used to treat gastritis and gastric ulcers. The mucin secretagogue activity of Mucosta® in addition to its anti-inflammatory and antibacterial effects suggests Mucosta® might improve the subjective symptoms of dry eye by upregulating membrane-associated-mucin expression. A multicenter, open-label study of 2% rebamipide in 154 dry eye patients showed that it improved signs and symptoms of dry eye after 2 weeks of treatment and up to at least 52 weeks compared with baseline, and was generally well-tolerated.[5]

These new treatments herald a new era of dry eye treatment based on the pathophysiology of dry eye. Because the pathophysiology of dry eye can be estimated by the dynamics of the tear film and disorders of the keratoconjunctival epithelium, the goal of TFOT has become clear. According to the tear film break-up pattern suggested by Yokoi [6,7], in spot area breaks, decreased wettability of the superficial epithelium is considered to be a major pathophysiological pathway. Diquas® and Mucosta® are expected to be effective for this type of dry eye disorder. In line breaks with moderate aqueous tear deficiency, Diquas® is expected to be most effective. Area breaks are associated with severe decreased aqueous tear production; thus, upper or lower punctal plugs are expected to be effective. Random breaks are a mild type of dry eye disorder that might respond to any artificial tears or hyaluronic acid.

In summary, the mechanisms of action of new dry eye treatments might target different pathophysiological pathways. Artificial tears replenish water and electrolytes; however, sodium hyaluronate, Cationorm®, and Diquas® improve tear film stability and conjunctiva epithelium disorders via different mechanisms. The concept of TFOT is to select the most suitable medical approach to improve tear film stability. In addition, the presence of inflammation should not be ignored because it is also a major pathophysiological pathway of dry eye. In most dry eye cases, anti-inflammatory drugs such as cyclosporine, steroids, and rebamipide can be incorporated into dry eye treatment as adjunctive therapy.

[1] Zheng X, et al. *Cornea* 2013;32:1260–4.
[2] Lin T, et al. *Drug Des Devel Ther.* 2015;9:687–94.
[3] Takamura E, et al. *Br J Ophthalmol.* 2012;96:1310–5.
[4] Gong L, et al. *Br J Ophthalmol.* 2015;99:903–8.
[5] Kinoshita S, et al. *Am J Ophthalmol.* 2014;157:576–83.
[6] Yokoi N, et al. *Future Medicine* 2013; 96–108.
[7] Yokoi N. *Journal of the Eye* 2015; 32:9–16.

Discussion

• CHAIRPERSON • **Dr. Zuguo Liu** Xiamen Eye Centre of Xiamen University, China

• DISCUSSANTS • **Dr. Louis Tong, Dr. Shizuka Koh, and Dr. Xiaoming Yan**

• There are two types of mucin: membrane-associated mucin and secretory mucin. Which type does Diquas® induce? What is your experience of Diquas® in dry eye patients?

Dr. Tong: Diquas® is not available for normal use in Singapore, only for clinical trials.

Dr. Koh: Diquas® induces secretory mucin and the best indication is for aqueous-deficient dry eye such as mild or moderate cases of dry eye with Sjögren's syndrome and short-break-up time dry eye.

• Dr. Tong showed similar incidence of dry eye between young and old groups but did not discuss baseline disease or past history of disease. Social behavior (extended use of cell phones or computers) of the young age group might be involved in the development of dry eye.

Dr. Tong: We showed that the higher socioeconomic group was independently associated with a higher prevalence, but not incidence, of dry eye after adjusting for multiple variable factors. The behaviors you mentioned may be more common among individuals in the higher socioeconomic group, irrespective of age.

• Dr. Tong's study showed the incidence of dry eye in adult Malays 40–79 years was lower than that in the US Beaver Dam study. Why?

Dr. Tong: The between-study differences are probably caused by different definitions of dry eye. Comparing different study designs is difficult. Previous reports showed a prevalence of 16–17% (based on one question, spanning a period of 3 months). We showed a prevalence of 6–10% and incidence of 5% (based on six questions, spanning a period of 1 month). Prevalence should be higher than incidence measured by the same definition because cases have an entire lifetime to develop dry eye whereas incidence studies are limited to a 5-year period. Therefore, our study findings are probably correct.

• New treatment for dry eye focuses on lipid, aqueous, and mucin layers to improve tear film stability. What are your opinions on the importance of mucin?

Dr. Koh: Inducing mucin secretion improves tear film stability, which leads to repair of ocular surface damage. The measurement of mucin levels in clinics might help us to evaluate the efficacy of Diquas® and other eye drops.

Dr. Tong: Dr. Koh mentioned that Japanese fashion magazines advertise mucin drops, indicating increased interest among the general public for dry eye treatment.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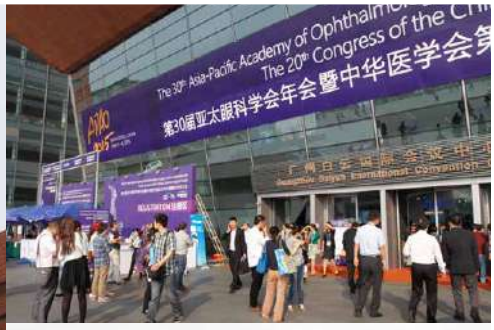
The 20th Congress of the Chinese Ophthalmological Society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