Professor Special Lecture: 152nd Regular Meeting of the Medical Society of Toho University

Review Article

Social Contribution of Ophthalmologists through Dry Eye Research

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ABSTRACT: Currently, the Department of Ophthalmology of Toho University is engaging in various types of research with the aim of contributing to society. One of the areas of our research is DRY EYE. There are over an estimated 10 million patients with dry eye in Japan, and the number is believed to keep increasing, thus suggesting the extreme importance of research on dry eye treatments.

Our research team has focused on mucins, one of the components of the tear film along with water and lipids. In Japan, diquafosol tetrasodium and rebamipide, two mucin secretagogue eye drops, are used as first-choice drugs to treat dry eye. When we compared these two drugs, we found that the secretion of tears promoted by these drugs had different characteristics. These studies made it possible to differentiate how these two drugs are used depending on the dry eye conditions.

The author is one of the organizers of the Japan Dry Eye Society. The Japan Dry Eye Society revises the definition and diagnostic criteria of dry eye every 10 years, conducts academic activities as well as promotes awareness on the importance of tears and dry eye treatment to the people of Japan. Through the efforts of the Dry Eye Society, July 3rd was established as "Tears Day" in 2017. We have held various events associated with "Tears Day," and hope to continue to make social contributions through our work and involvement in the field of dry eye research and treatment.

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KEYWORDS: ophthalmologist, social contribution, dry eye, mucin, Japan Dry Eye Society, Tears Day

Introduction

I graduated from the Osaka University School of Medicine in 1995 and started my residency as an ophthalmologist in the Osaka University Hospital. It has been over 23 years since I became an ophthalmologist. Recently, I began to ponder in particular "How we, as ophthalmologists, can contribute to society." Ophthalmologists are specialists of a very small sensory organ called the eye. Eighty percent of information that humans process is understood to consist of visual information that is taken in through the eye; thus, the profession of an ophthalmologist is an occupation of responsibility, as it involves treating an organ that is linked directly with people's quality of life (QOL). Our treatment of eye diseases enables people to live a richer life by enabling them to

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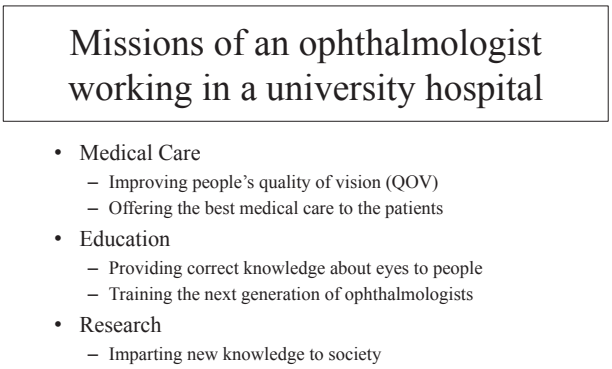

Fig. 1 Missions of ophthalmologist working in a university hospital.

maintain a higher quality of vision (QOV). Through our work at a university hospital, our mission of ophthalmologists not only involves surgery or medication to treat eye diseases (medical care). We also believe that promoting awareness of correct knowledge to the people, training the next generation of ophthalmologists (education), and transmitting new information to society through various research activities (research) to be important parts of our mission (Fig. 1).

We were given the opportunity to give a Professor Special Lecture at the 152nd Regular Meeting of the Medical Society of Toho University on June 15th, 2018. At the lecture, we showed the results of our experiments conducted at the Department of the Ophthalmology of Toho University to discuss the ways in which we, as ophthalmologists, can contribute to society. The theme that we discuss here is research on DRY EYE. The data shown here are, of course, not gathered by myself alone; it is the fruit of collaborative research that has been conducted by numerous peers and joint researchers. Our successful results in clinical research have been made possible only by the cooperation of our numerous patients. I would like to take this opportunity to express my sincerest gratitude to everyone who has cooperated in our research.

Dry Eye

Dry eye is a common ophthalmic disease. Dry eye is estimated to affect more than 10 million people in Japan. In particular, today, the widespread use of smartphones and computers, the increased number of people who wear contact lenses, and the pervasiveness of air conditioning are all contributing to the ever increasing number of patients with dry eye. The Japan Dry Eye Society, of which I am a member of organizers, revises the definition and diagnostic criteria of dry eye every 10 years since 1995.[1–3] The newest Japanese definition of dry eye revised in 2016 is as follows: "Disease characterized by decreased stability of the tear film caused by various factors, ocular discomfort and visual dysfunction, and may involve defects of the ocular surface."[3] As shown in this definition, the core mechanism of dry eye consists of "tear film instability."[3,4] Thus, the treatment for dry eye depends on how well the tear film can be stabilized. Various researchers have been conducting research on dry eye treatment over many years.

Ocular Surface Mucin

Sufficient water, lipids, and mucin, the main components of the tear film, are essential for stabilizing the tear film on the surface.[5] Mucins are polymeric glycoproteins, and MUC5AC, a mucin secreted from goblet cells in the conjunctiva, and MUC1, MUC4, and MUC16, membrane-associated mucins expressed in the corneal and conjunctival epithelial cells, are understood to be important for the ocular surface.[5–7] We have been researching on factors that regulate the expression of mucins found in the ocular surface and have reported previously that vitamin A (retinoic acid), serum, and phospholipids, such as phospholipase A2, are involved in the expression of membrane-associated mucins (MUC16).[8,9] Some contact lens solutions were reported to be able to reduce the expression of membrane-associated mucins on human corneal epithelial cells.[10,11] An in vitro experiment using the Rose Bengal penetrance assay[12] revealed that benzalkonium chloride contained in eye drops decreases the expression of membrane-associated mucins (Fig. 2). This suggests that clinically, it is associated with how the preservative benzalkonium chloride damages the membrane-associated mucins in the corneal and conjunctival epithelia in toxic keratoconjunctivitis.[13,14]

Mucin Secretagogue Eye Drops for Dry Eye

On the ocular surface, mucin serves important roles as a moisture preserver, barrier, and lubricant.[3] It has been reported previously that mucin expression on the ocular surface is decreased in patients with dry eye.[15–17] Much research has been conducted on mucin expression promotors as a treatment for dry eye, based on the idea that increasing mucin expression may treat dry eye.[18–20] For many years, treatments for dry eye in our country have

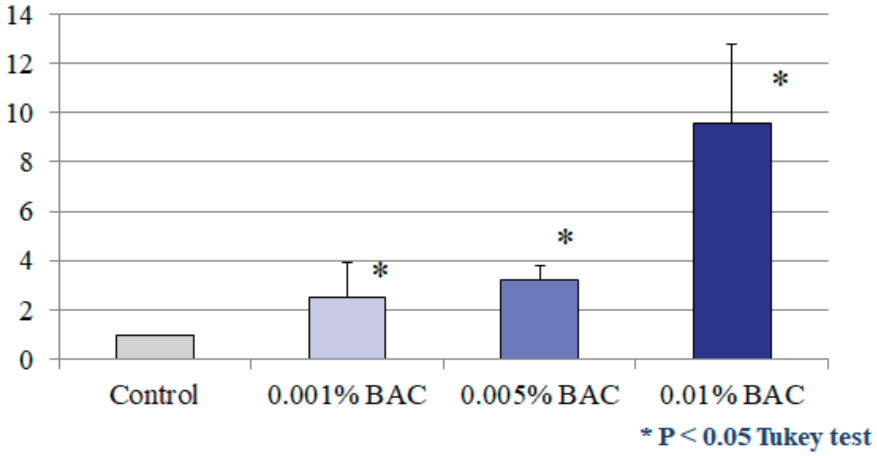

Fig. 2 To evaluate the disadhesive protective barrier function, a Rose Bengal dye penetrance assay was performed in a human conjunctival epithelial (HCjE) cell line as reported previously.[12] The cells then were exposed to 0.001%, 0.005%, and 0.01% benzalkonium chloride (BAC) for 1 minute. The area of the dye was increased significantly in cells with all BAC concentrations in a dose-dependent manner compared with the control (n = 5, P < 0.05, Tukey's test).

consisted exclusively of hyaluronic acid eye drops and artificial tears. Put simply, these treatments simply supplement moisture. However, after diquafosol tetrasodium[21] became commercially available in 2010, followed by rebamipide[22] in 2012, treatments for dry eye entered a new age. Both compounds promote the production of mucin, which is an important component of tears, and made it possible to treat the quality of tears. In addition to promoting the production of mucin, diquafosol tetrasodium promotes water secretion from the conjunctiva[21] and rebamipide has anti-inflammatory and mucosa-protective effects,[23,24] which makes it important to distinguish between the two in terms of use. To elucidate the pharmacological characteristics of diquafosol sodium and rebamipide, we compared the two eye drops in terms of water and mucin secretion.[25–27] In a trial studying tear secretion in normal rabbits, one dose of diquafosol sodium increased tear meniscus height significantly more than rebamipide for over 30 min.[25] An investigation on healthy individuals also demonstrated that diquafosol sodium increased tear volume more than rebamipide for 30 min after application.[26] An experiment on mucin secretion using normal rabbits showed that 15 min after administration, diquafosol sodium increased the secretion of MUC5AC, a secreted mucin, significantly more than rebamipide.[27] The above studies revealed that diquafosol sodium quickly increases moisture and mucin.

Dry Eye Society and "Tears Day"

The author is one of the organizers of the Japan Dry Eye Society (http://www.dryeye.ne.jp/). The chief organizer is Dr. Kazuo Tsubota, Professor of Ophthalmology at Keio University School of Medicine. This society was established in 1990 with the aims of promoting research on dry eye and of improving and promoting widespread treatments for dry eye. Thus far, the society has revised the definition and diagnostic criteria of dry eye every 10 years in 1995,[1] 2006[2] and 2016.[3] It has been conducting academic activities, as well as awareness activities in Japan to increase knowledge on the importance of tears and dry eye treatment. Since 2007, a two-day workshop called the "Hakone Dry Eye Club" has been held to present the research outcomes of dry eye and to train young dry eye researchers. Numerous globally leading studies from the Hakone Dry Eye Club have also been presented. Thus, Japan is truly a world leader in dry eye research. The fruitage of many years of Japanese dry eye research has been recognized, and a special issue focusing on Japanese dry eye research has been published in Investigative Ophthalmology & Visual Science in 2018 (Vol: 59, Issue 14).

The Dry Eye Society seeks to raise awareness on dry eye in Japanese people. July 3rd was established as "Tears Day" in 2017 after the approval of an application made to the Japan Anniversary Association. We hold

various related events on Tears Day as well as transmit information (http://namida-labo.jp/). For example, we developed a Dry Eye app for screening patients, and had participants of the Tears Day events use the app to study its effectiveness.[28] We have also conducted surveys to determine the general population's awareness of tears. We hope to continue our activities through "Tears Day" events so that Japanese people gain more thorough knowledge on tears.

Conclusions

To date, we have been contributing to society not only by treating patients who visit hospitals but also by protecting the ocular health of citizens through dry eye research. Today, many researchers of the Department of Ophthalmology of Toyo University are involved in research on dry eye as well as ocular circulation, pediatric ophthalmology, and infectious diseases. We hope to continue to serve society through our research in the field of ophthalmology.

Conflicts of interest: Y. Hori, Santen Pharmaceutical Co., Ltd. (F, C, R), Otsuka Pharmaceutical Co., Ltd. (F, C, R), Johnson & Johnson (F, C, R), HOYA (F), Alcon Japan Ltd. (F, R), Alcon Pharma (F, R), Senju Pharmaceutical Co., Ltd. (F, R), Kowa Pharmaceutical Co., Ltd. (F, R)

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Specialty

Ocular Surface Diseases, Dry Eye, Corneal Infection, Corneal Transplantation

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