The role of Rebamipide ophthalmic suspension in management of dry eye disease

Laxmi Dorennavar[1,*], Rajendra P Maurya[2], Virendra P Singh[3], Mahendra K Singh[4], Kamya Sharma[5], Ritika Sharma[5]

[1,6]Junior Resident, [5]Senior Resident, [2]Assistant Professor, [3,4]Professor, Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi

***Corresponding Author:**
Email: seematalks@gmail.com

ABSTRACT

Purpose of review: *Review of the drug Rebamipide, an ophthalmic suspension, in the treatment of dry eye and other ocular surface disorders.*

Method: *An extensive literature search was done on articles published in various ophthalmic journals to review the work on the latest drug rebamipide and its role in treating dry eye and other ocular surface disorders.*

Recent Findings: *Rebamipide is a novel drug for the treatment of dry eye disorders. It is a mucin-secretogogue, has a cytoprotective, anti-inflammatory effect and also suppresses the detrimental oxygen free radicals and helps in faster healing of epithelium. No major side effect has been noticed apart from dysguesia.*

Summary: *Rebamipide is the latest drug introduced in the treatment of dry eye. It seems to be a safe and effective treatment in chronic and severe forms of dry eye particularly due to mucus deficiency.*

Key Words: *Dry eye, Goblet cell, Microvilli, Rebamipide, Tear film*

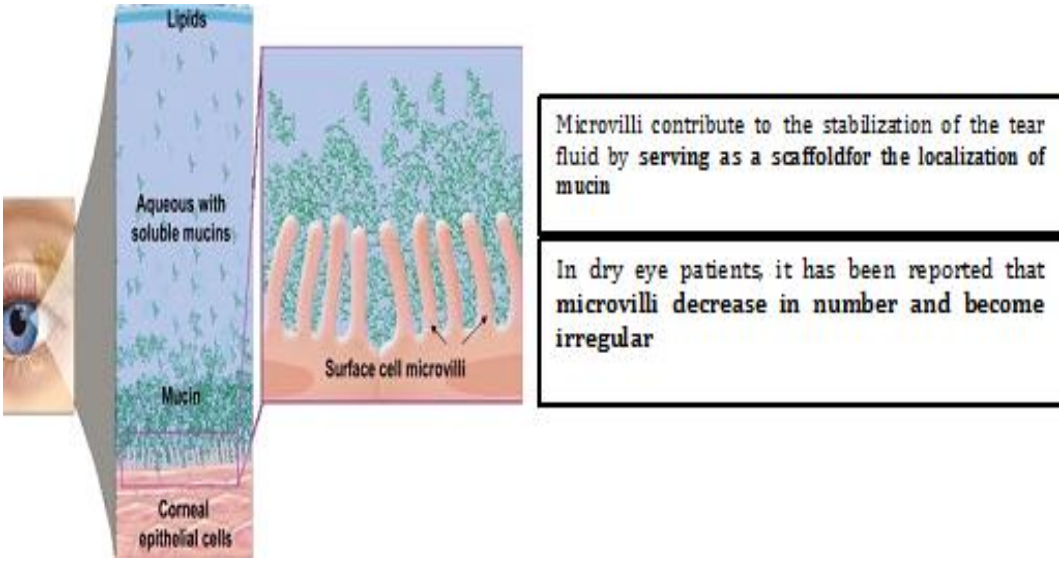
Access this article online	
Quick Response Code:	**Website:** www.innovativepublication.com
	DOI: 10.5958/2395-1451.2015.00025.6

INTRODUCTION

Dry eye as defined by International Dry Eye Workshop(DEWS) is a multifactorial disease of the tears and ocular surface causing symptoms of foreign body sensation, dryness, blurring of vision and photophobia and tear film/ instability[1]. Dry eye is a very common disorder encountered in daily ophthalmological practice commonly affecting females in menopausal age group and elderly patients. The cause of dry eye could be either aqueous deficiency which encompasses Sjogrens and Non-Sjogrens syndrome or due to excessive evaporation of tears due to defective tear film caused by improper mucin or lipids in tear film[2]. Apart from other factors which include aging, female gender, hormonal factors(low androgens), environmental factors (air conditioners, low humidity), lid abnormalities which prevent the spread of an even tear film and of late- the rising trend of refractive surgeries like LASIK. The prevalence is 5-16% as described in few studies in America and Australia while it is as high as 27-33% in Asian countries.[3] It has a negative impact on the patients quality of life, sometimes with potential sight threatening consequenc in long run if left untreated in few cases.[4,5]

Normal tear film:

The tear film is composed of an outermost lipid layer, a middle aqueous layer and an innermost membranous layer of mucins. Lipid secretion is by the meibomian glands, glands of Zeis and Moll forming 0.1µm of thickness.[6] These lipids are mainly of low polarity consisting of wax and cholesterol esters. Aqueous being secreted by the main lacrimal gland and accessory glands of Wolf ring and Krausse forms the middle layer measuring 10µm. The innermost layer is formed by mucin measuring 30µm, mainly secreted by the conjunctival goblet cells, glands of Manz and cypts of Henle. The presence of microvili on the epithelial layer and the glycocalyx present in mucin converts the hydrophobic epithelium to a hydrophilic one.[7] This layer plays an important role in maintaining the preocular tear film. It is on this surface that the aqueous and lipid layer evenly spreads out to produce a regular tear film. Lipid layer being the outermost prevents the evaporation of the tears.



Pathophysiology of dry eye:

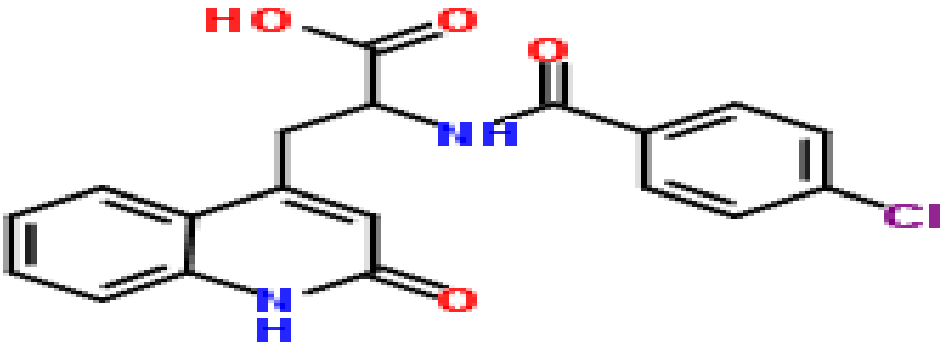
Dry eye can be caused due to either decreased aqueous, mucin or lipid production or excessive tear evaporation. This results in tear hyperosmolarity. A cascade of chronic inflammation sets in with the release of cytokines MAP (Mitogen-activated protein)kinases, NF-ķB (Nuclear factor –Kappa B), IL-1(Interlukin -1), TNF-α(Tumor necrosis factor) and MMP's(Matrix metalloproteinase) which in turn aggravate the condition of dry eye by causing tear film instability.[2,10]

Dry eye is a chronic disorder which requires a long term treatment. Tear substitutes, either preserved or non-preserved forms the mainstay of therapy in aqueous tear deficiency in mild to moderate dry eye disorder.[8,9] High viscosity lubricants and ointments are longer acting but cause blurring of vision.[11,12] Other options being autologous serum drops which has trophic factors essential for healing of epithelium, temporary or permanent punctual occlusion plugs,[13] oral secretogogues like oral pilocarpine and cevimeline. Meibomian gland disease causing lipid deficiency is treated with lid scrubs with mild shampoo, oral tetracycline and topical erythromycin /azithromycin and oral omega 3 fatty acid supplementation. Topical low dose steroids, topical cyclosporine act as anti-inflammatory agents to control ocular surface inflammation.[14]

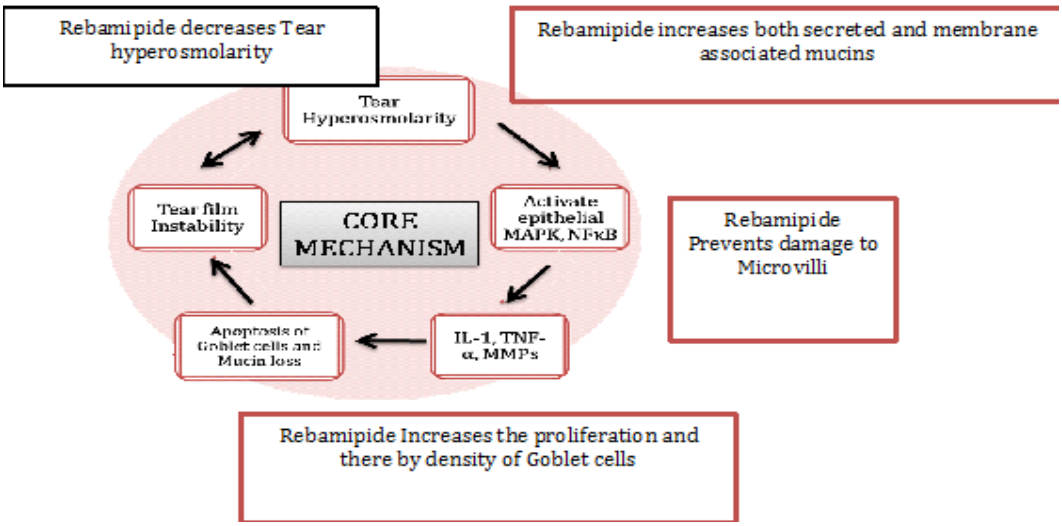
These various treatment modalities though address the evaporative and aqueous dry eye disorders but offer only a kind of maintenance therapy rather than providing a permanent cure. Preservatives present in tear substitutes like benzalkonium chloride, sodium perborate sodium chloride alter the tear osmolarity and frequent instillation of these drugs may cause more harm than doing good in cases of severe dry eye, where patients require frequent dosing.[15-7]

Rebamipide structure and mechanism of action:

Rebamipide is a new drug introduced in Japan in 2012 and is available as Mucosta ophthalmic suspension UD 2% for the treatment of dry eye; it is marketed by Otsuka pharmaceutical company. It is an amino acid analogue of 2 (1H)-quinolinone.[18-20]



The drug was initially introduced in 1980 for the treatment of peptic ulcer and is marketed as an oral drug with a dose of 100mg tablet containing 20% granules. It increases the gastric mucin production by increasing the synthesis of enzymes involved in production of high molecular weight glycoproteins and hence in healing of peptic ulcer due to its cytoprotective effect.[19-20] The same action works in dry eye disease where there is a component of decreased mucin production due to loss of conjunctival goblet cells as a result to chronic inflammation causing an impaired tear film stability.[21-24] The increased production of mucin is mediated by MUC1 and MUC4 gene expression. It also acts by decreasing production of oxygen radicals and superoxide ions by polymorphonuclear lymphocytes, increases local blood flow and production of protective prostaglandins in mucosa, which accelerates the process of epithelial healing. It also acts by suppressing the production of inflammatory cytokines like IL 8, TNFα and NFķB.[25,26]



Rebamipide in dry eye syndrome:

There have been several studies showing the effectiveness of rebapimide in treatment of dry eye syndrome. A significant improvement in Tear film break up time, Flourescein corneal staining (FCS) was seen along with improvement in subjective symptoms of dryness, foreign body sensation and photophobia has been noted.

A randomized, multicentre study, phase 3 trial was conducted by Kinoshita et al.[27,28] One hundred eighty patients with dry eye were randomly allocated to receive 2% rebapimide and 0.1% sodium hyaluronate eye drops for 52 weeks. Patients were followed up at weeks 2, 4 and later at every 4 weeks interval till the last time of visit by the patient. The efficacy of two drugs were compared as to the improvement in flourescein corneal staining score(FCSS), Lissamine Green conjunctival staining score (LGCS) and subjective symptoms relief. Results showed that 2% rebamipide showed significant improvement in Florescein corneal staining and Lissamine Green conjunctival scores whereas Tear film break up time and Schirmers were comparable to 0.1% sodium hyaluronate. Patients had a significantly more favorable

impression of 2% rebamipide(64.5% of patients) than of 0.1% sodium hyaluronate (34.7%) No serious adverse events were observed during this study period except for dysguesia. He concluded that administration of 2% rebamipide was effective in improving both the objective signs and subjective symptoms of dry eye.

The data from this present study are promising, showing that the efficacy and safety of preservative-free 2% rebamipide instilled 4 times daily is maintained for over 52 weeks. The patients also reported further improvement in both objective signs and symtoms at every visit. These findings suggested that 2% rebamipide may prove to be an excellent treatment option for patients with dry eye requiring long-term management. The most frequently observed adverse event for the rebamipide ophthalmic suspension in the study was dysgeusia (bitter taste); however, this was only observed in 9.7% of the 2% rebamipide group. The subgroup study conducted on patients with Sjogrens syndrome showed that the drug was more favourable in such patients who have decreased mucin production due to loss of goblet cells.

In a similar study, a retrospective case series study conducted at the department of ophthalmology at the Kobe university hospital in Japan by Ueda et al[29] recruited forty-eight eyes from 24 patients with dry eye between January 2012 and June 2012. All patients were prescribed 2% rebamipide ophthalmic suspension to be administered four times in a day and followed up for at least 12 weeks. Fluorescein ocular surface staining score (FOSS), Schirmer test, tear film break-up time (TBUT) and Dry eye-related symptom score were studied at 2, 4, 8, and 12 week visits. Results showed that there was significant improvement in the ocular staining score, Schirmers and TBUT improvement was noticed at every visit. TBUT showed significant improvement only after 8 weeks of treatment. Multiple regression analyses was done on independent variables and the study showed that there was a significant correlation of fluorescein ocular staining score with that of dry eye symptoms and vice versa, compared at baseline and after 12 weeks of treatment. Among symptoms, significant improvement was seen in foreign body sensation, dry eye sensation and ocular discomfort at all time of visits. The only side effect that was seen was dysguesia. It was noted that the improvement in symptoms was more consistent in patients with severe flourescein ocular stain score at baseline and severe dry eye features at presentation.

Arimoto et al**[30]** studied the effect of this drug in patients with Sjogrens Syndrome-Kerato conjunctivitis Sicca Syndrome.30 patients of SS-KCS with positive anti –SS/A-Ro and anti-SS/B confirmed with lip biopsy were enrolled and divided into three subgroups – only rebamipide, one puntum occlusion with rebamipide and both puncta occlusion with rebamipide. Fluorecein staining score, LSS, TBUT were evaluated at baseline and at 2 and 4 weeks. Results showed that there was significant improvement in all the three groups. With 4 weeks of treatment with rebamipide ophthalmic suspension, the signs and symptoms of moderate to severe SS-KCS improved significantly. Although SS-KCS is an aqueous deficiency type of dry eye disease, decreased levels of secretory mucins has been studied which explains the results of the drug – rebamipide in this group of patients.[31]

Koh et al**[32]** studied the role of rebamipide in the quality of vision in patients with dry eye who have mucin deficiency. The authors reported an improvement in the optical quality due to stabilisation of the tear film by mucin production by rebamipide.

Rebamipide in dry eyes due to anti-glaucoma drugs:

Dry eye has also been seen in patients with long term use of anti-glaucoma medication due to presence of preservatives like BAK.[33-36] Antiglaucoma eye drops are associated with a decrease in lacrimal fluid and disturbances in corneal epithelial barrier function. Tokuda et al[37] examined the efficacy of ophthalmic rebamipide suspensions on ocular surface disorders induced by antiglaucoma eye drops. In this randomized prospective study, forty eyes of 40 patients received latanoprost (0.005%) and timolol (0.5%) and were randomised in two groups- rebamipide receiving group and a control group. Patients receiving rebamipide showed significantly improved TBUT at 8 weeks (partially at 4 weeks) and improved corneal epithelial barrier function(both at 4 and 8 weeks), with no effect on IOP. Results suggested that rebamipide can be used to treat drug-induced ocular surface disorders.

Rebamipide in allergic conjunctivitis:

Rebamipide has also been tried in patients with VKC with giant papillae who had no improvements with topical steroids and immunosuppressives for a long time. Rebamipide exerts anti-inflammatory effects on the ocular surface by suppressing the polyI C-induced production of chemokines like CXCL10, CXCL11, RANTES (Regulation and activated normal T cell expressed and secreted), MCP-1 (Monocyte chemotactic protein -1), and IL-6 in human conjunctival epithelial Cells and protects corneal epithelial cells from the TNF induced disruption of barrier function by maintaining the distribution and expression of ZO-1as well as the organization of the actin cytoskeleton. Case reports by Ueta M et al[38] suggests that the combination of rebamipide eye drops and conventional anti-allergic treatments andor immunosuppressive steroid eye drops may represent a new effective therapy for VKC/AKC refractory to the usual anti-allergic treatments and that rebamipide eye drops may also be effective in the treatment of not only dry eye but also allergic conjunctival diseases.

CONCLUSION

From the clinical experience as stated above, rebamipide has been seen to be a novel drug with vast applications in dry eye syndrome, ocular surface disorders and allergic conjunctivitis. The safety profiles of the drug, in/ long term, as shown by few studies seem to be remarkable. It can be a great asset in treating patients with chronic and severe ocular surface disorders as compared to the present day treatment options since it is known to greatly improve the ocular surface and tear film stability both.

REFERENCES

1. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop (2007). Ocul Surf 2007;5:75–92.
2. American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry Eye Syndrome. Limited revision. San Francisco, CA: American Academy of Ophthalmology; 2011. Available at: http://one.aao.org/CE/PracticeGuidelines/PPP.aspx. Accessed July 26, 2012.
3. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. Clin Ophthalmol 2009;3:405–12.
4. Friedman NJ. Impact of dry eye disease and treatment on quality of life. Curr Opin Ophthalmol 2010;21:310–6.
5. Reddy P, Grad O, Rajagopalan K. The economic burden of dry eye: a conceptual framework and preliminary assessment. Cornea 2004;23(8):751–761.
6. Wolff, E.: Mucocutaneous junction of lid margin and the distribution of the tear fluid.trans.ophthal.Soc.U.k.66:291-308,1946.
7. Holly, F.J. and Lemp, M, A.: Tear Physiology And dry Eyes.Surv.Ophthalmol.22:69-87,1977.
8. Tear film- Lemp MA. Tear film: new concepts and implications for the management of the dry eye. Trans New Orleans Acad Ophthalmol. 1987;35:53–64.
9. Asbell PA. Increasing importance of dry eye syndrome and the ideal artificial tear: consensus views from a roundtable discussion. Curr Med Res Opin 2006;22:2149 –57.
10. Luo, D.-Q. Li, A. Doshi, W. Farley, R. M. Corrales, and S.C. Pflugfelder, "Experimental dry eye stimulates production of inflammatory cytokines and MMP-9 and activates MAPK signalling pathways on the ocular surface," *Investigative Ophthalmology & Visual Science*, vol. 45, no. 12, pp. 4293–4301, 2004.
11. Shimmura S, Ono M, Shinozaki K, et al. Sodium hyaluronate eye drops in the treatment of dry eyes. Br J Ophthalmol 1995; 79:1007–11.
12. Condon PI, McEwen CG, Wright M, et al. Double blind, randomised, placebo controlled, crossover, multicentre study to determine the efficacy of a 0.1% (w/v) sodium hyaluronate solution (Fermavisc) in the treatment of dry eye syndrome. Br J Ophthalmol. 1999;83:1121–1124.
13. Slusser TG, Lowther GE. Effects of lacrimal drainage occlusion with non-dissolvable intracanalicular plugs on hydrogel contact lens wear. Optom Vis Sci 1998;75:330–8.
14. Sall K, Stevenson OD, Mundorf TK, Reis BL, CsA Phase 3 Study Group. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. Ophthalmology 2000;107: 631–9.
15. Albietz JM, Bruce AS. The conjunctival epithelium in dry eye subtypes: effect of preserved and non-preserved topical treatments. Curr Eye Res. 2001;22:8–18.
16. Baudouin C, Labbe A, Liang H, et al. Preservatives in eye drops: the good, the bad and the ugly. Prog Retin Eye Res 2010;29:312–34.35.
17. Burstein NL. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. Trans Ophthalmol Soc U K 1985;104(4):402–409.
18. Arakawa T, Kobayashi K, Yoshikawa T, et al. Rebamipide: overview of its mechanisms of action and efficacy in mucosal protection and ulcer healing. Dig Dis Sci. 1998;43:5S–13S.
19. Y. Naito and T. Yoshikawa, "Rebamipide: a gastrointestinal protective drug with pleiotropic activities," *Expert Review of Gastroenterology and Hepatology*, vol. 4, no. 3,pp. 261–270, 2010.
20. K. Yamasaki, T. Kanbe, T. Chijiwa, H. Ishiyama, and S. Morita, "Gastric mucosal protection by OPC-12759, a novel antiulcer compound, in the rat," *European Journal of Pharmacology*, vol.142, no. 1, pp. 23–29, 1987.
21. Takeji Y, Urashima H, Aoki A, et al. Rebamipide increases the mucin-like glycoprotein production in corneal epithelial cells. J OculPharmacol Ther. 2012;28:259–263.
22. Danjo Y, Watanabe H, Tisdale AS, George M, Tsumura T, Abelson MB, et al. Alteration of mucin in human conjunctival epithelia in dry eye. Invest Ophthalmol Vis Sci. 1998;39:2602–9.
23. Rios JD, Shatos M, Urashima H, Tran H, Dartt DA. OPC-12759 increases proliferation of cultured rat conjunctival goblet cells. Cornea. 2006;25:573–81.
24. Itoh S, Itoh K, Shinohara H. Regulation of Human Corneal Epithelial Mucins by Rebamipide. Curr Eye Res. 2013;39:133–41.
25. Ueta M, Sotozono C, Yokoi N, Kinoshita S. Rebamipide suppresses Poly I: C stimulated Cytokine production in human conjunctival epithelial cells. J Ocul Pharmacol Ther. 2013;29:688–93.
26. H. Tanaka, K. Fukuda, W. Ishida, Y. Harada, T. Sumi, and A. Fukushima, "Rebamipide increases barrier function and attenuates TNFα-induced barrier disruption and cytokine expression in human corneal epithelial cells," *The British Journal of Ophthalmology*, vol. 97, no. 7, pp. 912–916, 2013.
27. Kinoshita S, Awamura S, Nakamichi N, Suzuki H, Oshiden K, Yokoi N. Rebamipide Ophthalmic Suspension Long-term Study Group. A Multicenter, Open-Label, 52-Week Study of 2% Rebamipide (OPC-12759) Ophthalmic Suspension in Patients with Dry Eye. Am J Ophthalmol. 2014;157:576–83.
28. Kinoshita S, Oshiden K, Awamura S, Suzuki H, Nakamichi N, Yokoi N. Rebamipide Ophthalmic Suspension Phase 3 Study Group. Ophthalmology. 2013;120:1158–65.
29. Kaori Ueda, Wataru Matsumiya*, Keiko Otsuka, Yoshifumi Maeda, Takayuki Nagai and Makoto Nakamura, "effectiveness and relevant factors of 2% rebamipide ophthalmic suspension treatment in dry eye", BMC Ophthalmology (2015) 15:58 DOI 10.1186/s12886-015-0040-0.
30. A. Arimoto, K. Kitagawa, N. Mita, Y. Takahashi, E. Shibuya, and H. Sasaki, "Effect of rebamipide ophthalmic suspension on signs and symptoms of keratoconjunctivitis sicca in Sj¨ogren syndrome patients with or without punctal occlusions," *Cornea*, vol. 33, no. 8, pp. 806–811, 2014.
31. Argueso P, Balaram M, Spurr-Michaud S, Keutmann HT, Dana MR, Gipson IK, et al. Decreased levels of the goblet cell mucin MUC5AC in tears of patients with Sjogren syndrome. Invest Ophthalmol Vis Sci. 2002;43:1004–11.
32. Koh S, Inoue Y, Sugmimoto T, Maeda N, Nishida K. Effect of rebamipide ophthalmic suspension on optical quality in the short break-up time type of dry eye. Cornea. 2013;32:1219–23.

33. J. M. Herreras, J. C. Pastor, M. Calonge, and V. M. Asensio, "Ocular surface alteration after long-term treatment with an anti-glaucomatous drug," *Ophthalmology*, vol. 99, no. 7, pp. 1082–1088, 1992.
34. E. W. Leung, F. A. Medeiros, and R. N. Weinreb, "Prevalence of ocular surface disease in glaucoma patients," *Journal of Glaucoma*, vol. 17, no. 5, pp. 350–355, 2008.
35. R. D. Fechtner, D. G. Godfrey, D. Budenz, J. A. Stewart, W. C. Stewart, and M. C. Jasek, "Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications," *Cornea*, vol. 29, no. 6, pp. 618–621, 2010.
36. A. Niiya, N. Yokoi, Y. Matsumoto et al., "Effect of beta-blocker eye drops on corneal epithelial barrier function," *Ophthalmologica*, vol. 214, no. 5, pp. 332–336, 2000.
37. Naoto Tokuda, Yasushi Kitaoka, Akiko Matsuzawa, Junsuke Miyamoto, Shinsuke Sakae, Yasunari Munemasa, and Hitoshi Takagi, "The Effect of Rebamipide on Ocular Surface Disorders Induced by Latanoprost and Timolol in Glaucoma Patient", Hindawi Publishing Corporation Journal of Ophthalmology Volume 2015, Article ID 689076,
38. Mayumi Ueta, Chie Sotozono, Ayaka Koga, Norihiko Yokoi and Shigeru Kinoshita, "Usefulness of a New Therapy Using Rebamipide Eye drops in Patients with VKC/AKC Refractory to Conventional Anti-Allergic Treatments", *Allergology International.vol63 2014;63:75-81.*