

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

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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-secretoagogue, 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

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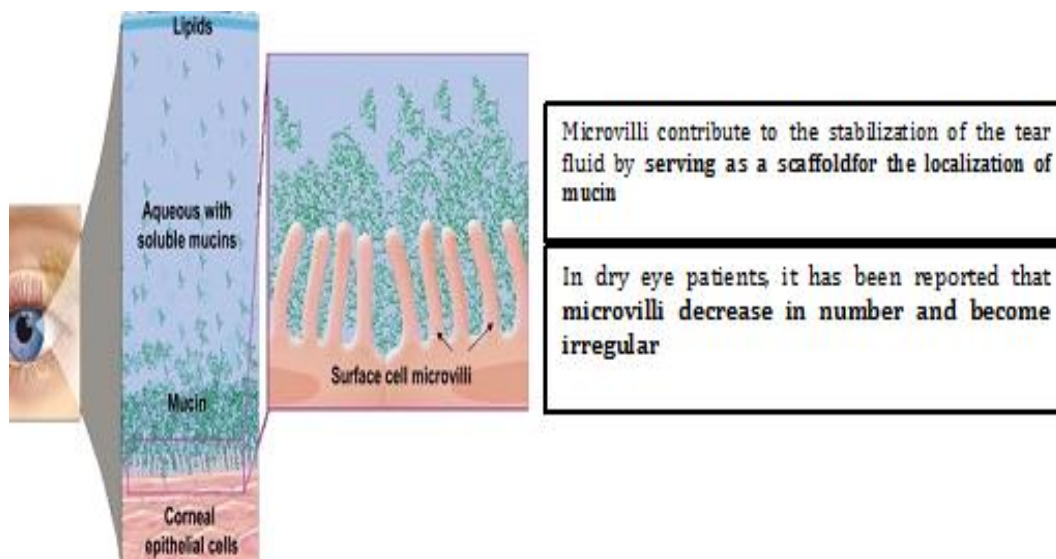
INTRODUCTION

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 Krause 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:

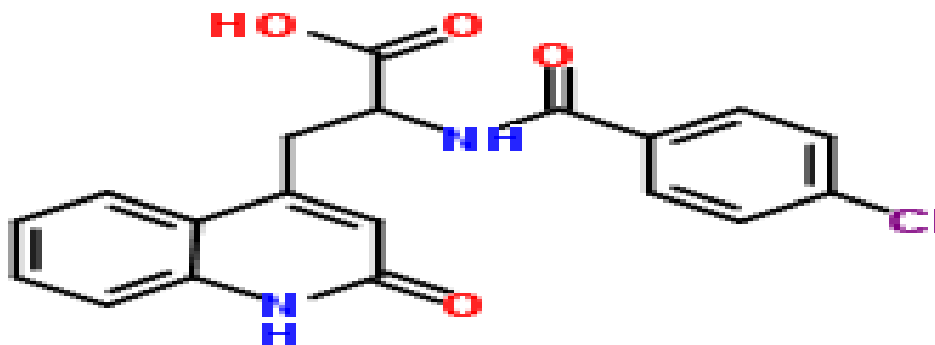
Dry eye can be caused due to either decreased aqueous, mucin or lipid production or excessive tear evaporation. This results in tear hyperosmolality. A cascade of chronic inflammation sets in with the release of cytokines MAP (Mitogen-activated protein)kinases, NF- κ B (Nuclear factor –Kappa B), IL-1(Interlukin -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]

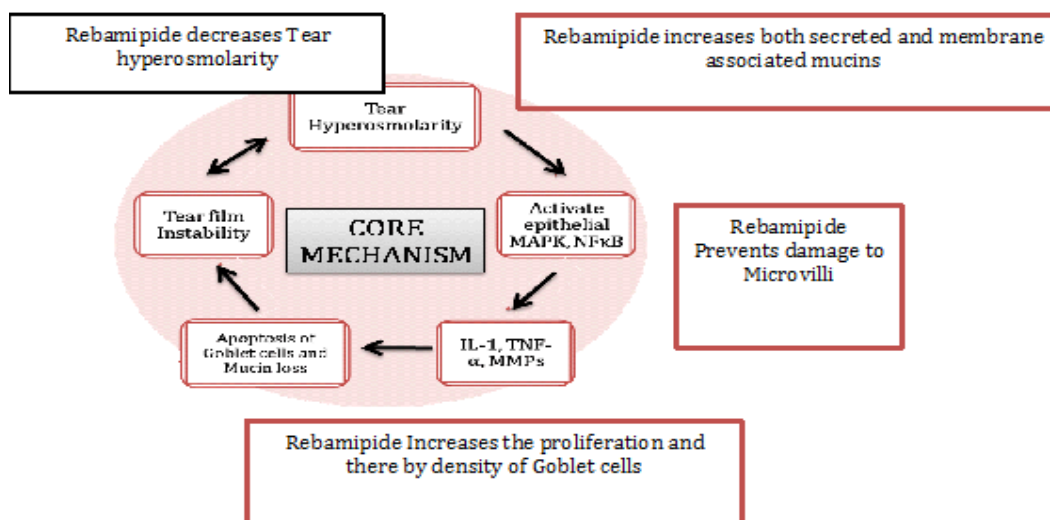
These various treatment modalities though address the evaporative and aqueous dry eye disorders but offer only a kind of maintenance therapy rather than providing a permanent cure. Preservatives present in tear substitutes like benzalkonium chloride, sodium perborate sodium chloride alter the tear osmolality 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, TNF α and NF κ B.^[25,26]



Rebamipide in dry eye syndrome:

There have been several studies showing the effectiveness of rebamipide in treatment of dry eye syndrome. A significant improvement in Tear film break up time, Fluorescein 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% rebamipide 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 fluorescein 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 dysgeusia. 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 symptoms 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 dysgeusia. It was noted that the improvement in symptoms was more consistent in patients with severe fluorescein 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 punctum occlusion with rebamipide and both puncta occlusion with rebamipide. Fluorescein 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-1 as 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 and/or 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.

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