Rebamipide 2% Ophthalmic Suspension for the Treatment of Allergic Keratoconjunctivitis: A Hospital Based Study

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Abstract

Background: The aim of this study was to evaluate the effectiveness of Rebamipide 2% ophthalmic suspension in the treatment of Allergic Keratoconjunctivitis. Rebamipide 2% ophthalmic suspension has shown to be advantageous for the treatment of dry eye and an improvement of ocular allergic conditions, after its application is also remarkable for the patients, especially in severe conditions. Study was done to report the improvement in signs and symptoms after using Rebamipide 2% as an additional therapy in allergic patients and reduced dependency on topical steroids.

Materials and Methods: Rebamipide 2% ophthalmic suspension was used in the treatment of allergic keratoconjunctivitis. We used subjective signs and symptoms of allergic keratoconjunctivitis as well as objective tests of tear film production like TBUT and Schirmer I and compared the post-treatment values at 1 week, 3 weeks, 5 weeks and 7 weeks, with baseline values.

Results: The study revealed that Rebamipide 2% significantly improved the clinical grading of the disease, Schirmer I and Tear Film Breakup Time (TBUT) scores. No significant side effects to the therapy were observed. In steroid responsive patients, no aggravation of symptoms was observed after tapering the dose of steroids while steroid non-responder patients showed a significant improvement in the clinical signs and symptoms of allergic keratoconjunctivitis. Maximum effect was observed at 5 weeks of initiation of therapy.

Conclusion: Rebamipide 2% is effective in improving the signs and symptoms of allergic ocular diseases and is well-tolerated. It helps in reducing the dependence on steroids for the treatment of allergic keratoconjunctivitis.

Keywords: rebamipide, allergic keratoconjunctivitis, vernal keratoconjunctivitis

Background

Rebamipide 2% is a novel quinolinone derivative (Figure 1). It has been shown to increase gastric endogenous prostaglandin E2 and I2, promote gastric epithelial mucin, is an oxygen free radical scavenger and has other anti-inflammatory actions as well.¹ In addition to its use for the gastrointestinal mucosa, the biological effects of rebamipide 2%, which include cytoprotection, wound healing, and anti-inflammatory properties, are known to be universal for a variety of tissues. In 1994, gastric mucosal lesions (erosion, haemorrhage, erythema, and edema) associated with gastritis were subsequently added to its indications. Since then, it has been widely used as a therapeutic agent for gastritis and gastric ulcers.² After discovering the pharmacological actions of rebamipide 2%, began its development for use as a dry eye medication. In nonclinical studies, it was shown that Rebamipide 2% increases corneal and conjunctival mucin, and conjunctival goblet cells.³,⁴ Also it is known that Rebamipide 2% increases the mucin production in cultured conjunctival goblet cells and in corneal epithelial cells.⁵,⁶ Studies have shown that Rebamipide 2% has an improving effect not only on corneal and conjunctival epithelial damage, but also on subjective symptoms.⁷-¹⁰ Based on these results, Rebamipide 2% was launched in January 2012 for the treatment of dry eye in Japan (Mucosta ophthalmic suspension unit dose 2%). It was also shown in a study that rebamipide suppressed polyI:C- induced inflammatory cytokines in human conjunctival epithelial cells¹¹ and Kimura et al documented that rebamipide protects corneal epithelial cells from TNF-α induced disruption of barrier function by maintaining the distribution and expression of ZO-1 as well as organization of the actin cytoskeleton.¹² It also suppressed the TNF induced expression of interleukin-6 and interleukin-8 at mRNA.¹³ Hence, suggesting some adjunct role of this drug in suppression of mediators of inflammation in cases of allergic...
eye diseases. In this paper, we studied the use of this drug in the management of patients with allergic conjunctivitis refractory to conventional anti-allergic treatment.

Materials and Methods

Study design- Prospective Study

Ethical considerations

An informed consent was obtained from the patient prior to recruitment. The study did not involve any invasive procedure. All therapeutic decisions were taken by the treating physician and no interference was done. Confidentiality of patient was maintained and patients or his/her relative had the right to opt out of study at any given point of time. The study was conducted at G.G.S. Medical College and Hospital, Faridkot. Thirty eyes of 15 patients diagnosed with allergic conjunctivitis on long term steroids (at least 3 months) attending outpatient department were randomly selected. A detailed history of disease and prior treatment was taken. Based on their response to steroids, the patients were divided into two groups: steroid responsive & steroid non-responsive. Steroid responsive patients included the ones which showed improvement in their signs and symptoms while on steroid therapy while non-responders were the ones who did not show any change in their symptomatology despite getting full therapeutic steroid dosage at least for 6 weeks.

All the patients were instructed to instil Rebamipide 2% eye drop 4 times a day, 1 drop at a time in combination with the anti-allergic treatment till the next follow up. The drug was available in the market in the name of “Fine Tears” manufactured by Akumentis Healthcare Limited. The follow up was done at 1 week, 2 weeks, 5 weeks and 7 weeks of initiating the treatment. At each follow up visit, a slit lamp photograph was taken and following findings were noted:

- Decrease in subjective symptoms such as dryness, discomfort, foreign body sensation, redness, itching, pain, and visual symptoms like blurring and photophobia.
- Decrease in signs of ocular surface inflammation like conjunctival injection, papillae, chemosis and discharge. Size and number of papillae was noted in all cases on every visit and any decrease in size of papillae or area of involvement was taken into consideration.
- Improvement in tear production was noted with Schirmer I test. The Schirmer’s test was performed without anaesthesia to measure tear volume as follows - A Schirmer’s test strip was placed on the lower eyelid (between the eyelid conjunctiva and the bulbar conjunctiva) without touching the cornea. The tear volume was then measured for 5 minutes after the patient was instructed to close the eyelid lightly. The length in millimetres of tear fluid absorbed on the strip measured from the edge of the strip is recorded.
- TBUT (Tear Film Breakup Time) was measured in all patients by following method - Fluorescein strip containing impregnated sodium fluorescein dye was used to stain the conjunctiva and Slit-lamp evaluation was done using cobalt blue filter. The time from normal blinking to the first appearance of a dry spot in the tear film was measured.
- Dose of steroid eye drops was gradually tapered for all the patients after starting rebamipide eye drops and any side effects to the therapy were noted on every visit.
- Effect of weaning off the steroid eye drops was noted.
- Efficacy was evaluated by comparing pre-treatment/ baseline score to post-treatment scores by using following grading system: (Table I)

Statistical analysis

IBM SPSS statistical software version 21 was used for statistical analysis. Data was expressed as mean plus minus standard error and evaluated by student T test using Microsoft excel.

Results

A total of 15 patients (30 eyes) participated in the study. Study blinding was maintained throughout, and no important protocol deviations were observed. All 15 patients who received treatment were included in the efficacy and safety analysis. Rebamipide 2% eye drops response was observed at 1 week, 2 weeks, 5 weeks and 7 weeks after the pre-treatment baseline tests conducted on the day of 1st visit. Out of 30 (60 %) eyes had dry eyes as tested with Schirmer-I and TBUT test. Following observations were made for various clinical aspects:

Subjective signs and symptoms

Out of 15 patients, 9 patients (18 eyes) were steroid responsive however, whenever the drug was tapered, the symptoms and signs relapsed. After starting these patients on Rebamipide eye drops and simultaneous tapering of steroid eye drops, no relapse in signs and symptoms in any of these cases was observed at 1 week. At 3rd week, steroids were completely withdrawn in 3 out of 9 patients. On subsequent visits, no

| Table 1: Clinical grading of patients according to severity of symptoms |
|------------------|------------------|------------------|------------------|
| **Grade**        | **1**            | **2**            | **3**            | **4**            |
| Discomfort, severity and frequency | Mild/ episodic, under environmental stress | Mod episodic/ chronic, stress or no stress | Severe frequent/ constant without stress | Severe and/or disabling and constant |
| Visual symptoms  | None/episodic. Mild fatigue | Annoying/ activity limiting, episodic | Annoying, chronic/ constant, limiting activity | Constant/ possibly disabling |
| Conjunctival injection | None to mild | None to mild | +/- | +/- |
| Corneal staining | None to mild | Variable | Marked central | N/a |
| Corneal/ tear signs | None to mild | Mild debris | Filamentary keratitis, mucus clumping | Ucleration |
| Lid/meibomian glands | MGD variably present | MGD variably present | MGD frequent | Trichiasis, keratinisation, symblepharon |
relapse of disease was observed. Remaining 6 patients were steroid non-responders i.e. no improvement even after taking full therapeutic dosage of steroids. However, Schirmer-1 and TBUT score showed normal values i.e. no dry eye in these patients except for one case. Rebamipide 2% eye drops instilled 4 times a day in these patients showed a significant improvement in their signs and symptoms after 5 weeks of starting with the drops after which steroids were eventually tapered and no worsening in symptoms observed. There was a constant trend towards improvement in clinical grading seen in all patients irrespective of the baseline pre-treatment values. More patients were found in grade 1 or no symptoms at all at 5 weeks post-treatment with rebamipide 2%. (Figure 2)

Overall, an improvement in the mean clinical grading was observed in all the cases after starting rebamipide eye drops. (Figure 3). Objective tests like TBUT and Schirmer I also showed significant improvement.

Schirmer’s Test
The baseline Schirmer I scores were 10.5 and 28.6 in patients with dry eye (Schirmer <15) and no dry eye (Schirmer >15) respectively. A significant difference (p<0.05) between the mean scores at 1 week (12.3 and 30.5 respectively), 3 weeks (9.1 and 16.4 respectively), 5 weeks (10.1 and 16.7 respectively) and 7 weeks (11.0 and 17.1 respectively) post-treatment with rebamipide 2% eye drops. (Figure 5)

Tear Film Break-Up Time
The mean TBUT values at baseline were 6.1 and 14.2 in patients with dry eye (TBUT <10) and no dry eye (TBUT >10) respectively. There was a significant difference (p<0.05) between the mean scores at 1 week (6.7 and 15.3 respectively), 3 weeks (9.1 and 16.4 respectively), 5 weeks (10.1 and 16.7 respectively) and 7 weeks (11.0 and 17.1 respectively) post-treatment with rebamipide 2% eye drops. (Figure 5)

Patients’ Overall Treatment Impressions
There was a statistically significant improvement in patients’ overall treatment impressions in all the groups.

Safety Evaluation
There were no drug related adverse effects noted in any of the patients.

Discussion
Our study suggested that rebamipide 2% eye drops might contribute to the reduction in symptoms and signs of Allergic keratoconjunctivitis and Vernal keratoconjunctivitis. Rebamipide 2% has been used to treat gastritis and gastric ulcers. It suppresses gastric mucosal inflammation and increases gastric mucus production. We postulated that rebamipide 2% eye drops improve tear production and quality as seen with Schirmer I and TBUT. The results demonstrated that treatment with rebamipide 2%, which presents a treatment option with a novel mechanism of action, was associated with improvements in both corneal and conjunctival parameters of dry eye and allergic conditions. These findings were corroborated by a recent study showing that rebamipide 2% increased the number of Periodic Acid-Schiff reagent–positive cells in the conjunctiva when instilled at concentrations of 0.3% or higher, and rebamipide 2% increased the amount
of mucin-like substances of the conjunctiva and cornea in normal rabbits. A recent report also observed a significant increase in a mucin-like glycoprotein and MUC1 and MUC4 gene expression after human corneal epithelial cells were incubated with rebamipide 2%. However, an exact mechanism of action in allergic cases has not been evaluated so far. Possibly, an improvement in the ocular surface morphology leads to subsidence of allergic signs in these patients. Therefore, these data suggest that improvement of keratoconjunctival epithelium disorders as well as allergic disorders namely vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) with rebamipide 2% may be due to an increase of mucin and improvement in surface epithelium. Encouraging results in objective signs were also supported by favourable data obtained in subjective symptoms (foreign body sensation, dryness, photophobia, eye pain, redness and blurred vision) and patients’ overall treatment impression. Such improvements in subjective symptoms should contribute to improved quality of life in patients with allergic disorders and less dependency on long term steroid therapy especially in children. Similarly, Ueta et al recently in Japan conducted a clinical trial of this drug on 4 patients with VKC/AKC refractory to conventional anti-allergic treatment and observed attenuation of the giant papillae in all 4 patients, thereby, for the first time demonstrating the use of this drug for allergic conjunctival diseases. Reported adverse event rates were null in the study. Maximum benefit among all the patients was found by at least 3-5 weeks of treatment with rebamipide 2%. However, there are certain limitations to this study as the sample size was too small and follow up was short.

Conclusion

The rebamipide 2% ophthalmic suspension was launched in January 2012 in Japan. Published data has shown that this drug has been advantageous for the treatment of dry eye, as compared to older drugs currently being used, including lubricants. In our clinical experience, the improvement of ocular allergic conditions after its application is remarkable even in severe cases. Rebamipide 2% was effective in treating both objective signs and subjective symptoms of allergic ocular diseases and was well tolerated in this 7 week study. Overall, these findings confirm our belief that topical rebamipide 2% may become the drug of first choice for some cases of dry eye syndrome and as an adjunctive therapy in allergic diseases. Moreover, we believe that, in the future, this drug has a great potential to markedly reduce the demand for harmful immunosuppressives required for long term therapy in these patients.

References

1. National Centre for Biotechnology Information. Pubchem CompoundDatabase;CID=5042;https://pubchem.ncbi.nlm.nih.gov/compound/5042.

2. Tomoyuki Kashima, Hirotaka Iikura, Hideo Akiyama, Shoji Kishi. Rebamipide 2% ophthalmic suspension for the treatment of dry eye syndrome: A critical appraisal. Clin Ophthalmol 2014; 8:1003–10.

3. Mantelli F, Argüeso P. Functions of ocular surface mucins in health and disease. Curr Opin Allergy Clin Immunol 2008; 8:477–83.

4. Takeji Y, Nakashima H, Kagawa Y, Urashima H, Shinohara H. Effect of rebamipide 2% ophthalmic suspension on capsaicin-induced corneal epithelial damage in rats. Atarashii Ganka 2013; 30:1309-13.

5. 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.

6. Rios JD, Shatos MA, Urashima H, Dartt DA. Effect of OPC-12759 on EGF receptor activation, p44/p42 MAPK activity, and secretion in conjunctival goblet cells. Exp Eye Res 2008; 86:629–36.

7. Takeji Y, Urashima H, Aoki A, Shinohara H. Rebamipide 2% increases the mucin-like glycoprotein production in corneal epithelial cells. J Ocul Pharmacol Ther 2012; 28:259–63.

8. Urashima H, Okamoto T, Takeji Y, Shinohara H, Fujisawa S. Rebamipide 2% increases the amount of mucin-like substances on the conjunctiva and cornea in the N-acetylcycteine-treated in vivo model. Cornea 2004; 23:613–9.

9. 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.

10. Takeji Y, Urashima H, Aoki A, Shinohara H. Rebamipide 2% increases the mucin-like glycoprotein production in corneal epithelial cells. J Ocul Pharmacol Ther 2012; 28:259–63.

11. 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.

12. Kimura K, Morita Y, Orita T, Haruta J, Tkeji Y, Sonoda KH. Protection of human corneal epithelial cells from TNF-alpha induced barrier disruption and cytokine expression in human corneal epithelial cells. British Journal Ophthalmol 2013; 97:912-6.

13. Tankha H, Fukuda K, Ishida W, Harada Y, Sumi T, Fukushima A. Rebamipide increases barrier function and attenuates TNF alpha induced barrier disruption and cytokine expression in human corneal epithelial cells. British Journal Ophthalmol 2013; 97:912-6.

14. Urashima H, Takeji Y, Okamoto T, Shinohara H. Rebamipide 2% increases mucin-like substance contents and periodic acid Schiff reagent-positive cells density in normal rabbits. J Ocul Pharmacol Ther 2012; 28:259–70.

15. Takeji Y, Nakashima H, Kagawa Y, Urashima H, Shinohara H. Rebamipide 2% increases the amount of mucin-like substances on the conjunctiva and cornea in the N-acetylcycteine-treated in vivo model. Cornea 2004; 23:613–9.

16. 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.