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Research Article

The Study of Rebamipide for the Treatment of Vernal Keratoconjunctivitis at a Tertiary Care Center in North India

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Abstract

Background: Vernal Keratoconjunctivitis (VKC) is a severe form of allergic conjunctivitis characterized by persistent ocular surface inflammation. It has symptoms associated with allergies and dry eye. We aim to evaluate the efficacy of Rebamipide in the treatment of individuals with moderate to severe vernal keratoconjunctivitis.

Methods: The present study is a prospective, analytical, single-center study conducted at a tertiary care center for a period of 18 months. A total of 510 eyes of 270 patients with VKC were included. Patients were randomly selected and assigned from the eye OPD for the study. Patients received Rebamipide eye drops [2% w/v], 1 drop QID for the treatment of VKC. The effects of Rebamipide on the symptoms and signs were evaluated in follow-ups.

Results: A comprehensive evaluation of the treatment efficacy of Rebamipide 2% eyedrops in patients with VKC reveals notable improvements in both symptoms and signs. Specifically, when comparing the Total Subjective Symptom Scores (TSSS) assessing patient-reported discomfort, itching, tearing and visual disturbances, there was a marked reduction from the baseline to the scores recorded after 12 weeks of treatment. Additionally, the Total Objective Sign Scores (TOSS), which included clinical evaluations of conjunctival redness, papillary formation and discharge, also demonstrated significant improvement over the same period. Statistical analysis of the relevant data yielded a p-value of 0.0001, indicating a highly significant difference and affirming the efficacy of Rebamipide 2% eyedrops in managing the symptoms and signs of VKC over the 12-week treatment duration.

Conclusion: Our findings suggest that the efficacy of topical Rebamipide administered in the eyes of patients suffering from VKC was effective in reducing signs and symptoms.

Keywords: Vernal Keratoconjunctivitis; VKC, Rebamipide; TSSS; TOSS; Ocular Allergy

Introduction

Rebamipide 2% ophthalmic suspension was a novel quinolinone derivative, invented as a drug to protect the gastric mucosa by increasing the production of gastric mucus and inhibit the inflammatory reaction of the gastric mucosa [1-4]. A study conducted by Urashima, et al., stated that Rebamipide causes upregulation of secretion and production of mucin on the ocular surface [5]. In Japan, Rebamipide eyedrops are well-approved for the management of dry eye conditions. Kinoshita S, et al., stated that rebamipide 2% w/v eyedrops were well tolerated by Vernal Keratoconjunctivitis (VKC) patients, effectively improving the signs and symptoms of dry eye components [6-8]. Patients with allergic conjunctival disease and dry eye symptoms showed an improvement in Tear Film Breakup Time (TFBUT) after using rebamipide eyedrops [9,10]. In certain lab studies, Rebamipide 2%

was shown to increase the production of mucin in the conjunctiva and the number of conjunctival goblet cells [11,12]. It is also known to increase mucin production in conjunctival goblet cells and corneal epithelial cells [13-15]. Several comprehensive studies have shown that Rebamipide 2% has not only improved the status of conjunctival and corneal epithelium but also made an overall symptomatic improvement [16-18]. In a detailed and illuminating study, Kimura, et al., demonstrated that Rebamipide 2% plays a protective role in preserving the integrity of corneal epithelial cells that have been compromised by TNF-alpha-induced disruption of barrier function. The authors highlighted how Rebamipide effectively sustains the distribution and expression of Zonula Occludens-1 (ZO-1), a critical marker for tight junctions, while also promoting the proper organization of the actin cytoskeleton. This multifaceted action underscores the potential therapeutic benefits of Rebamipide in maintaining corneal cellular stability and function under inflammatory conditions [19]. A study documented that Rebamipide 2% suppresses TNF-alpha-induced expression of interleukin-6 and interleukin-8 at mRNA [20]. Another alternative mechanism of rebamipide to help in the management of VKC is that it suppresses poly C-induced inflammatory cytokines in the epithelium of human conjunctiva [21]. In response to the impressive results of clinical trials, Rebamipide 2% was officially launched in January 2012 as a groundbreaking treatment for dry eye syndrome in Japan. This innovative therapy offers relief to countless individuals suffering from this condition, marking a significant advancement in ophthalmic care. The application of rebamipide eye drops, particularly in conjunction with traditional antiallergic medications, has been demonstrated to improve therapeutic outcomes in the treatment of vernal and atopic keratoconjunctivitis. This combination therapy is especially advantageous for patients who do not adequately respond to standard antiallergic treatments, immunosuppressive agents or steroid therapies. By incorporating rebamipide, clinicians may achieve better results for individuals suffering from these challenging allergic ocular conditions [22]. VKC is a prevalent and persistent allergic condition affecting the eyes, commonly exhibiting seasonal patterns. This chronic disorder is characterized by recurrent inflammatory episodes of cornea and conjunctiva, often resulting in a variety of symptoms, ie, ocular discomfort, redness, intense itching, tearing, grittiness, foreign-body sensation and in chronic cases, patients may present with diminution of vision (Table 1). Interestingly, some individuals may experience these episodes without any noticeable symptoms, making VKC a complex condition that can occasionally go unrecognized [23]. Patients of VKC usually begin to exhibit symptoms during the early years of life, typically between the ages of 5 and 10 and primarily affects boys. As they progress into their teenage years, around the ages of 10 to 20, the severity of symptoms may gradually decline for some individuals. This decrease in symptomatology can vary widely among patients, with some continuing to experience allergic episodes during pollen seasons or in response to environmental triggers. Overall, while VKC tends to improve with age, ongoing monitoring and management may be necessary to address any persistent or recurrent symptoms [24]. There is significant regional and racial variability in this disease. It is most prevalent and severe in hot, dry climates such as the Mediterranean, West Africa and the Indian subcontinent. While Vernal Keratoconjunctivitis (VKC) is uncommon in temperate regions, approximately 90% of patients also suffer from other atopic conditions, such as eczema and asthma and about two-thirds have a family history of atopy [25]. VKC is typically triggered by exposure to environmental allergens such as pollen grains, household dust, mites and animal dander. These allergens trigger immunologic response activation, specifically involving Immunoglobulin E (IgE) and cell-mediated responses, which play a crucial role in its pathogenesis [26]. VKC presents in both mild and severe chronic forms and is characterized by its bilateral and recurrent nature. As VKC can significantly impact the quality of life, understanding its mechanisms and manifestations is essential for effective management. The treatment options for underlying inflammatory and allergic responses are the use of antihistamines, mast cell stabilizers like olopatadine, lodoxamide, sodium cromoglycate, nedocromil and Nonsteroid Anti-Inflammatory Drugs (NSAIDs) like nepafenac, bromfenac, flurbiprofen, ketorolac and corticosteroids to alleviate inflammation and control symptoms [27]. This serious disease predominantly affects school-aged children between the ages of 6 and 14 and is becoming increasingly prevalent in northern India, especially in the state of Uttar Pradesh. Therefore, many children face challenges in their studies, which can hinder their academic progress and limit future opportunities. Furthermore, the disease also affects their social skills and emotional well-being, diminishing the joy and carefree spirit that are vital to their youth. The rising incidence of this condition is a significant concern for both families and educators, underscoring the urgent need for effective interventions and support systems [28]. Despite significant advancements in our understanding and treatment options, a long-term solution continues to be elusive. Current therapies primarily concentrate on reducing short-term inflammation. For moderate to severe and resistant cases of VKC, treatment options include immunotherapeutics such as Cyclosporine and tacrolimus and ganglioside derivatives like mipragoside, as well as the promising new agent Rebamipide. These are typically used in conjunction with topical steroids, mast cell stabilizers and topical NSAIDs [29]. Regrettably, most of these treatment approaches are comparatively ineffective in severe, refractory VKC. Newly introduced Rebamipide eyedrops provide hope for the management of VKC cases where dry eye-related symptoms are more marked. Therefore, the treatment of this disease and the relief of symptoms are very stressful for both the patient and the treating

physician. The patience of patients is strained by frequent hospital visits.

Materials and Methods

A prospective, randomized, double-blinded, comparative clinical study was designed. An informed consent form was thoroughly explained and obtained from the patient before their enrolment in the study, ensuring they understood the purpose and procedures involved. The study was designed to be non-invasive. All therapeutic decisions were exclusively made by the patient's treating physician, with no external interference from the research team, thereby prioritizing the patient's health and well-being. Confidentiality was strictly maintained throughout the study, with all personal and medical information securely protected. Additionally, the patient and their relatives were informed of their right to withdraw from the study at any point without any repercussions, reinforcing their autonomy and ensuring they felt comfortable with their participation. The ethical clearance was taken from the hospital ethics committee of Uttar Pradesh University of Medical Sciences, Saifai Etawah. Diagnosis of VKC was made clinically according to the presence of classical signs and symptoms. The clinical Scoring System of Bleik, et al., (Table 1) was used to grade the signs and symptoms. The guardians of verbal children or adolescents with active disease, that is, total subjective symptom score, TSSS > 6 and total objective sign score, TOSS > 4, presenting in the outpatient department (OPD) were explained in the study. Those who agreed to the regular follow-ups were included after taking proper written informed consent. In this study, 270 patients were enrolled. The sample size of the present study was 270, based on the incidence and prevalence of VKC in India. A total of 510 eyes of 270 patients with VKC were selected, based on the inclusion and exclusion criteria. Patients aged 4 to 20 years with symptoms and signs suggestive of vernal keratoconjunctivitis were included. The following are the inclusion criteria for the enrolment of patients: Patients having confirmatory signs and symptoms for diagnosis of Vernal Keratoconjunctivitis and Patients in the age group of 4-20 years. Following are the exclusion criteria for the present study: Individuals who have had previous eye surgery, patients with only one eye, eye trauma, co-existing eye diseases (such as glaucoma, uveitis or corneal disease), lactating women, pregnant women, contact lens wearers, individuals allergic to any of the ingredients or individuals who have had the punctal plug removed within the past three months. The patient's name, age and sex were noted. The eye in which the study was performed was also noted. A detailed history was taken, including the duration of symptoms, chronicity of the disease and its character (seasonal, perennial, first episode). Any associations, including keratoconus and limbal stem cell deficiency or any other atopy history (bronchial asthma, eczema, allergy, family history of allergy) were noted. Systemic diseases such as diabetes mellitus and hypertension were also recorded. Previous treatment of ocular disease, including the name of the drug, duration of use and duration of discontinuation of the drug before taking the study drug, was noted. All enrolled patients received Rebamipide eye drops [2% w/v] 1dp QID to evaluate the effect of Rebamipide eye drops in first and subsequent follow-ups. Transient ocular symptoms caused by the medications, such as burning, stinging, eye pain, periorbital edema, periorbital rash and headache, were assessed within 30 minutes of medication administration and graded from 0-3 according to severity. The main outcome was measured by the Total Subjective Symptom Score [TSSS] and the Total Ocular Sign Score [TOSS] before and after treatment at each visit. Patients took the medication for 12 weeks and follow-ups were conducted at 1 week, 3 weeks, 6 weeks and 12 weeks. A thorough ocular examination was conducted at the start, each visit and at the end of the study, to assess the size and number of papillae, number of Horner's trantas points, visual acuity, refraction, keratometry, eye movements and slit lamp examination. Distance visual acuity was measured at 6 meters using Snellen's visual acuity chart. Intraocular pressure was measured before the procedure using a Tonopen Reichert tonometer. The type of vernal kerato-conjunctivitis was described according to the site where it occurs (tarsal, limbal, mixed). Symptoms and signs were measured using a Bleik grading system (Table 2) of 0-3, representing zero, mild, moderate and severe. Patients in the study rated their symptoms after receiving an explanation of the rating system. The symptoms identified included itching, tearing, discharge, redness, a foreign body sensation, pain and photophobia. Meanwhile, a masked ophthalmologist evaluated and graded the signs. The assessment focused on the eyelids, conjunctiva, limbus and cornea. The eyelid sign specifically noted was eyelid edema, while the conjunctival signs included hyperemia, discharge and chemosis. Papillae were classified as null, micro, macro and giant (0-3). Limbal and corneal signs were marked as present or absent. Limbal signs were limbal hyperplasia and Horner's trantas dots. The corneal signs recorded were thyroid ulcer, epithelial keratitis and pannus. A detailed examination of the anterior segment of the eye was performed with the ZEISS slit lamp. Papillae were noted on the eversion of the tarsal plate and corneal involvement was noted after staining with a fluorescein 1 mg strip moistened with lubricant. Other ocular findings in the anterior chamber and pupil were observed and lens status was recorded. Fundus dilation using a 90-diopter lens with slit lamp biomicroscopy was performed and the cup-disk ratio was noted. Finally, the effect of the drug was analyzed in the enrolled patients.

Itching	0=no desire to scratch 1=intermittent desire to scratch 2=frequent desire to scratch 3=constant desire to scratch
Discomfort/Foreign Body Sensation	0=no foreign body sensation 1= discrete similar to dust 2= mild similar to sand 3= severe constant similar to rock
Photophobia	0=o photophobia 1=mild squints in bright light 2=Moderate improve with use of sunglasses 3=sever improve with total eye occlusion
Tearing	0= absent 1=humid no epiphora 2=intermittent epiphora 3=constant epiphora

Table 1: Clinical scoring system (Bleik, et al.,). Severity score of symptoms of VKC [11]; Total Subjective Symptoms Score (TSSS) [4].

Conjunctival Hyperemia	0= calm conjunctiva 1=mild increase in vessel diameter, difficult to notice 2=moderate increase in diameter and number of vessels 3=diffuse and intense hyperemia
Upper Tarsal Papillae	0=no central tarsal vessel 1=central tarsal vessel present 2=some giant papillae 3=giant papillae predominant
Discharge	0=no discharge 1=little amount in fornix 2=moderate amount in the fornix 3=sticky eyes in morning
Keratitis	0= no epitheliopathy 1=superficial punctate keratitis 2=confluent punctate keratitis 3=shield ulcer
Shield Ulcer	0= no evidence, 1= one quadrant 2= (two quadrants 3= (three or more quadrants)
Trantas Dots	0= (no dots), 1= (1 to 2 dots) 2= (3 to 4 dots),3= (more than 4 dots)
Limbus Infiltration	0= no infiltration 1= < 90°of limbal infiltrate 2=< 180°but >90° 3= >180° of limbal infiltrate

Table 2: Severity score of signs of VKC Total Objective Ocular Sign Score (TOSS) [4,11].

Results

Table 3 The data indicate a notable male preponderance in the prevalence of the disease, with a significant concentration among children aged 6 to 10 years, yielding a mean age of 10.2 years and a standard deviation of 4.05 years. According to the modified Kuppuswamy scale, most patients fall into the upper-lower socioeconomic class, followed closely by those identified in the lower socioeconomic class. In terms of clinical presentation, the limbal form of VKC emerges as the most prevalent type within the

study population, outpacing the mixed form, while the palpebral form is observed to be the least common variant. Interestingly, most patients in the cohort do not exhibit any accompanying systemic allergic conditions. However, when such associations do exist, they predominantly manifest as allergic rhinitis, asthma and atopic dermatitis, with allergic rhinitis and asthma being more frequently observed than other systemic allergic diseases. This highlights the importance of monitoring for potential co-morbidities in patients diagnosed with VKC, especially during the critical developmental years.

		N	%
Gender	Male	175	64.8
	Female	95	35.2
Age Group	Less than equal 5	25	9.3
	6 to 10	138	51.1
	11 to 15	68	25.2
	16 to 20	39	14.4
Age	Range	4 to 20	
	Mean ± SD	10.3 ± 4.05	
Locality	Rural	174	64.4
	Urban	96	35.6
Socioeconomic Status	Upper	0	0.0
	Upper middle	14	5.2
	Lower Middle	55	20.4
	Upper lower	112	41.5
	Lower	89	33.0
Vkc Type	Limbal	135	50.0
	Palpebral	45	16.7
	Mixed	90	33.3
Associated Allergic Conditions	Allergic rhinitis	45	16.7
	Asthma	44	16.3
	Atopic dermatitis	23	8.5
	No	158	58.5

Table 3: Demographic profile of cases.

Table 3 The incidence of Vernal Keratoconjunctivitis varies by age across different groups, with the highest prevalence occurring in the 6 to 10-year age bracket. In this age group, the limbal form is more common than the mixed form, while the palpebral form is the least prevalent type of VKC. The p-value of 0.006 indicates a statistically significant difference between age groups and the type of VKC.

Association Between Age Group and VKC Type							
		VKC Type			**Total**	**Pearson Chi-Square**	**p-value**
		Limbal	**Palpebral**	**Mixed**			
Age Group	Less than equal 5	18	5	2	25	18.033	0.006
	6 to 10	75	15	48	138		
	11 to 15	26	18	24	68		
	16 to 20	16	7	16	39		
Total		135	45	90	270		

Table 4: Association between Age Group and VKC type.

Table 5 The gender distribution across various forms of VKC indicates that males are more frequently affected than females in all types of VKC. However, the p-value of 0.548 indicates that there is no statistically significant difference between sex and VKC type, suggesting that both males and females are equally susceptible to the different forms of VKC.

Association Between Sex and VKC Type							
		VKC Type			Total	Pearson Chi-Square	p-value
		Limbal	Palpebral	Mixed			
Sex	Male	84	32	59	175	1.202	.548
	Female	51	13	31	95		
Total		135	45	90	270		

Table 5: Association between sex and VKC type.

Fig. 1 the mean values of the Total Subjective Symptom Score (TSSS) and Total Objective Sign Score (TOSS) at baseline, as well as during subsequent follow-ups, particularly at the 12-week mark, indicate a significant reduction in both TSSS and TOSS. This finding suggests that Rebamipide eye drops are an effective topical treatment for managing Vernal Keratoconjunctivitis.

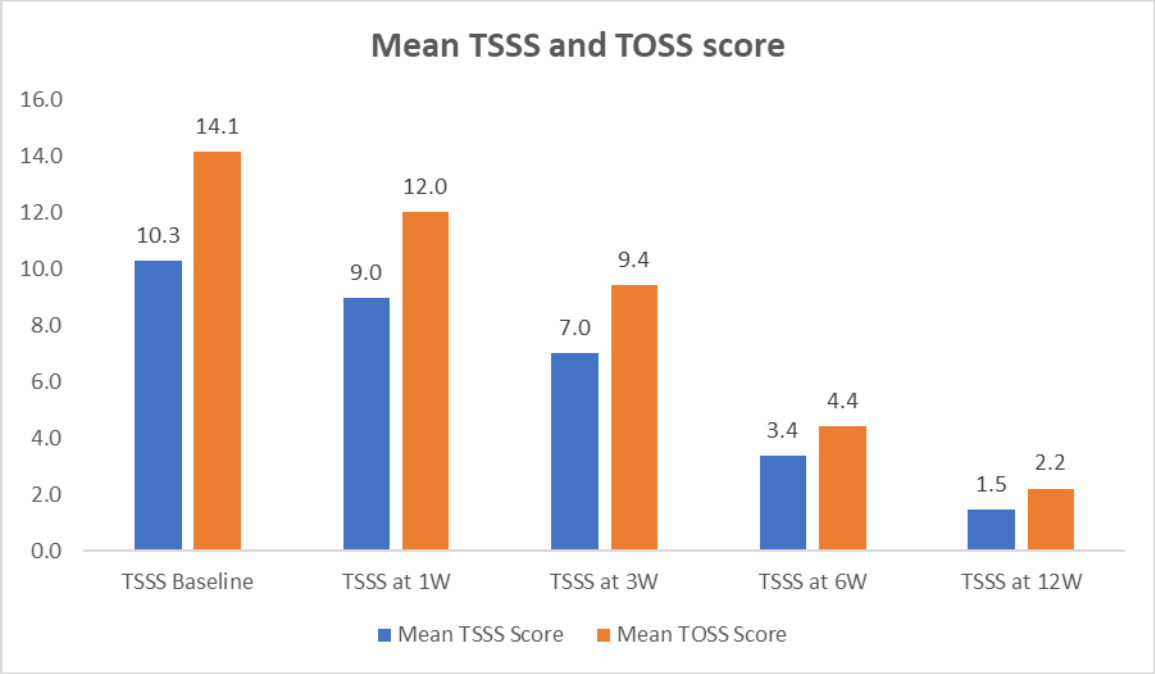

Figure 1: The mean values of the Total Subjective Symptom Score (TSSS) and Total Objective Sign Score (TOSS) at baseline.

Table 6 the Analysis of Variance (ANOVA) reveals compelling findings regarding the treatment of vernal keratoconjunctivitis with topical Rebamipide. Initially, the mean baseline TSSS (Total Subjective Symptom Score) is recorded at 10.29, reflecting a significant burden of symptoms. Remarkably, after a 12-week treatment period, this score diminishes to a mere 1.46, indicating a profound reduction in symptom severity. The P-value of 0.00001 underscores the statistical significance of this difference, strongly suggesting that topical Rebamipide is a highly effective therapeutic option for alleviating the symptoms associated with this ocular condition. Following a comprehensive post hoc analysis of the ANOVA, the findings reveal a noteworthy and significant difference in the mean scores of the Total Subjective Symptoms Score (TSSS) when compared to baseline measurements taken at the start of the study and again at the conclusion of the 12-week intervention period. This notable shift in scores indicates a significant change in participants' stress levels over the study's duration, highlighting the potential effectiveness of the Rebamipide eyedrop.

	Mean TSSS Score	Std. Deviation	p-value*
TSSS Baseline	10.29	1.77	0.00001
TSSS at 1W	8.96	1.356	
TSSS at 3W	6.99	1.196	
TSSS at 6W	3.37	0.877	
TSSS at 12W	1.46	0.556	

Table 6: ANOVA Test for evaluation of TSSS.

Discussion

Vernal Kerato-Conjunctivitis (VKC) can cause severe, debilitating symptoms in young people. The name "spring catarrh" comes from the fact that it is more common in the tropics and in the spring. A total of 270 patients (510 eyes) were included in the present study. All 270 patients who received treatments were included in the efficacy and efficiency analysis. The study reveals a male predominance of the disease, with the highest incidence observed in the 6 to 10 age group, averaging 10.2 years. According to the modified Kuppuswamy scale, most patients are classified in the upper lower socioeconomic class, followed by the lower class. Among the different forms of VKC, the limbal variant is the most common, while the mixed form follows and the palpebral form is the least frequent. Within specific age groups, the same order of prevalence has been observed (Table 3,4). Analysis of gender distribution in VKC shows that males are more frequently affected than females. However, with a p-value of 0.548, this difference is not statistically significant, indicating that both sexes have similar vulnerability to VKC's various forms (Table 5). Most patients do not have other systemic allergic conditions; however, when such associations do exist, they typically present as allergic rhinitis, asthma or atopic dermatitis, with allergic rhinitis and asthma being the most prevalent. In a comprehensive 7-week study, researchers examined the therapeutic potential of Rebamipide 2% in patients suffering from allergic ocular diseases. The findings revealed that this formulation not only effectively mitigated the objective signs but also significantly reduced the subjective symptoms of eye discomfort, including persistent itchiness and an overwhelming sensation of dryness reported by participants (Table 6). Recent findings indicate that Rebamipide 2% has an impressive safety profile, with very few side effects reported, which highlights its tolerability among patients. These results suggest that topical Rebamipide 2% could emerge as the preferred first-line treatment for certain cases of dry eye syndrome. Additionally, it may serve as an effective adjunct therapy for those suffering from allergic ocular conditions [30]. Recurrent VKC is a chronic eye condition mostly affecting children and young adults. It involves fluctuations in the immune response of the eye, often worsened by seasonal allergens like pollen and dust mites. This episodic inflammation can damage the ocular surface and negatively impact vision and eye health over time [24]. As recurrences of VKC decrease, patients often experience less photophobia and wind sensitivity. Improvements in tear film quality help protect the ocular surface and enhance visual clarity. Addressing recurrent VKC is crucial for immediate symptom relief and long-term ocular health [31]. Managing VKC requires a comprehensive approach that considers factors like the patient's age, symptom severity and chronicity. This complexity can challenge even experienced ophthalmologists, as treatment responses vary. Alongside pharmacological options, non-pharmacological strategies are essential. Identifying and avoiding triggers, such as pollen and dust, as well as adopting lifestyle modifications like good eye hygiene and protective eyewear during allergy seasons, can help alleviate symptoms. This holistic management aims to improve the overall quality of life for those affected by VKC [32]. To manage VKC effectively, use soothing artificial tears for immediate relief and apply cold compresses to reduce swelling. Stylish sunglasses can protect your eyes from UV rays and allergens. Most importantly, avoid exposure to allergens to diminish symptoms. Following these steps will help lessen discomfort, swelling and redness associated with VKC [33-35]. There are various therapeutic options for treating VKC, including antihistamines, mast cell stabilizers such as sodium cromoglycate, dual-acting combinations, alpha-adrenergic agonists (vasoconstrictors), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), immunomodulators (cyclosporin A, tacrolimus) and corticosteroids [36]. In 2008, Tacrolimus 1% ophthalmic suspension was approved. Since then, it has been widely used off-label with varying formulations at concentrations from 0.003% to 1.0% have shown significant improvement in signs and symptoms of VKC with negligible systemic absorption. Tacrolimus ointment is approved primarily as a second-line therapy for moderate to severe atopic dermatitis. Within this indication, only 0.03% concentration is indicated for use in children 2-15 years of age [37-44]. A combination therapy that employs a dual mechanism includes antihistamines and mast cell stabilizers to deliver both immediate and prolonged symptomatic relief for patients suffering from ocular allergies. Topical agents with this dual mechanism of action comprise olopatadine in concentrations of 0.1%, 0.2% and 0.7%, as well as bepotastine besilate at 1.5%, azelastine at 0.05% and alcaftadine at 0.2% [45]. Dupilumab, a humanized monoclonal antibody, acts as a leukotriene antagonist by blocking IL-4, IL-13 and Th2-mediated

inflammation, which are involved in the development of conjunctival papillae in ocular allergy [46]. Initially approved for severe, refractory atopic dermatitis, clinical trials have indicated an increase in conjunctivitis and keratitis among patients using dupilumab [47]. A claims database analysis of 2144 patients from January 1, 2016, to June 30, 2019, also noted more medical encounters for ocular surface disorders after starting the treatment [48]. A recent case reports suggest that patients with atopic conditions, severe Allergic Keratoconjunctivitis (AKC) and VKC treated with dupilumab experienced improvements in symptoms, including a reduction in the size of giant papillae [49-52]. Interleukin-5 plays a crucial role in the recruitment and activation of eosinophils, which are essential for inflammatory responses in the body. In the treatment of asthma and allergic ocular disorders, three monoclonal antibodies-benralizumab, mepolizumab and reslizumab-have emerged as effective therapies. Each of these treatments targets specific pathways within the immune system, offering a promising approach to alleviating symptoms associated with these conditions. Additionally, accumulating evidence indicates that these therapies may offer significant benefits in managing VKC and other ocular allergic conditions [53]. A newly introduced medication, Omalizumab, is a recombinant humanized monoclonal antibody that binds to free Immunoglobulin E (IgE), a key player in allergic reactions. While it is approved for severe persistent asthma, there are promising off-label uses for treatment-resistant VKC [54,55]. Recently, Ueta, et al., introduced the drug, Rebamipide, a quinolone-class derivative, which acts as a mucin secretagogue, enhancing protective mucin secretion. It reduces pro-inflammatory cytokines IL-6 and IL-8, decreases eosinophilic infiltration and inhibits TNF-α, a key inflammatory mediator [21]. Clinical studies show that Rebamipide effectively decreases papillary formation in patients with VKC and AKC, especially those unresponsive to traditional therapies. However, some patients may experience side effects like dysgeusia and eyelid pruritus [22]. Koh, et al., reported that rebamipide markedly enhances tear film breakup time. Their findings revealed significant improvements from baseline measurements, showcasing notable upward trends in total corneal higher-order aberrations, as well as reductions in both coma-like and spherical-like aberrations following the application of rebamipide [56]. Takahashi, et al., conducted a study revealing that patients with thyroid eye disease who also experienced Superior Limbal Keratoconjunctivitis (SLK) exhibited significant improvements after treatment with topical rebamipide. Remarkably, 84.8% of these patients experienced a complete resolution of SLK following the treatment. The authors concluded that topical rebamipide could potentially serve as a first-line therapeutic option for managing SLK in this patient population, highlighting its efficacy in addressing this challenging condition [57]. In a separate investigation, the application of topical rebamipide demonstrated significant effectiveness in alleviating corneal and conjunctival disorders associated with lid-wiper epitheliopathy. This study highlighted the agent's potential to improve ocular surface health and address the specific challenges presented by this condition [58]. In a separate case report, rebamipide was administered to patients with Sjögren's syndrome who exhibited erosion in the inferior cornea following surgical punctal occlusion. This treatment aimed to alleviate discomfort and promote healing in these individuals, addressing the complications that arose from their condition and the surgical intervention [59]. The study shows that rebamipide ophthalmic suspension effectively treats corneal epithelial damage from tear deficiency and low mucin levels. It helps restore the microstructure of corneal and conjunctival surfaces, enhancing tear film stability and reducing inflammatory reaction. The therapeutic effects were evaluated through improvements in subjective symptom scores and objective sign scores after 12 weeks (Graph 1), highlighting Rebamipide's potential to promote ocular health and comfort [60]. Based on Rebamipide's ability to modify conjunctival and corneal epithelial cell functions, the authors suggested that this may open new strategies for treating human ocular surface inflammation, including allergic conjunctivitis and dry eye diseases.

Conclusion

Rebamipide 2% ophthalmic suspension was launched in Japan, marking a significant advancement in the treatment of dry eye syndrome. Clinical studies demonstrate that it offers significant benefits over traditional therapies, such as lubricants. Our experience indicates that rebamipide effectively improves severe ocular allergic conditions, leading to a notable reduction in symptoms of Vernal Kerato-Conjunctivitis (VKC) after 12 weeks of treatment. It can be used as monotherapy or alongside other medications, with no serious adverse effects recorded. Overall, rebamipide proves to be an effective option for managing moderate to severe VKC and may reduce reliance on harmful long-term immunosuppressive therapies.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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