Effectiveness of a modified therapeutic protocol for the management of vernal keratoconjunctivitis based on Bonini's graded clinical severity

Anuradha Pradhan, Sabyasachi Pattanayak[1], Jayashree Dora[2], Praveen Subudhi[3]

Purpose: To evaluate the effectiveness of a modified therapeutic protocol used for vernal keratoconjunctivitis (VKC) based on severity as per Bonini grading system. **Methods:** This was a prospective observational clinical study conducted with 123 eyes of 63 patients. A meticulous clinical examination was performed, and data was documented in all the cases. Patients on known systemic atopy and antiallergic therapy were excluded from the study. Eyes with a clinical diagnosis of VKC were segregated based on Bonnini's grading system. A treatment protocol was created depending on the grade of VKC. Therapeutic responses were documented at 3 weeks, 3 months, 6 months, 12 months, and 24 months. Grading of the eyes was performed in each visit. **Results:** The mean age of the patients was 8.85 years with a standard deviation of 4.48 years. Males were predominant, and 95.24% had bilateral manifestation. The palpebral component was the most common form of manifestation. Itching was the most common manifestation, followed by congestion, discharge, and papillae in a decreasing order. Also, 68% of patients were in grade 2, 14% in grade 3, 12% in grade 1, and the rest were in grade 4. Following the treatment protocol, 70% showed signs of significant improvement in grade by the end of 6 weeks, reaching 90% at the end of 6 months ($P = 0.074$) and 92% at the end of 12 months ($P = 0.002$). Also, 52.4% versus 77.8% of patients had no recurrence in the pre- versus posttreatment protocol and it was statistically significant ($P = 0.001$). **Conclusion:** Grading of VKC gives a clear evaluation of the severity and progression of the condition. Besides, significant improvement in the grades was observed with fewer incidences of recurrences following execution of the therapeutic protocol. Hence, it is essential to maintain a treatment protocol in our clinical practice to provide grade-based therapy and monitor accurate changes in the clinical condition.

Key words: Bonnini's Grading, vernal keratoconjunctivitis, VKC

Vernal keratoconjunctivitis (VKC) is a chronic, often bilateral, and severe form of allergic inflammatory condition of the ocular surface, seen mostly in boys <10 years of age.[1] It has a typical seasonal occurrence during spring, aggravation in summer, and remission in autumn and winter, but may present perennially in some with exacerbations during spring and summer.[2] The disease often resolves spontaneously after puberty, but may result in permanent damage of cornea in some due to shield ulcers, infectious keratitis, keratoconus, corneal opacities, and limbal stem cell deficiency affecting vision significantly, if not treated properly.[3]

The typical clinical symptoms of VKC include intense itching, redness, lacrimation, photophobia, sticky mucus discharge, and presence of giant papillae on the upper tarsal conjunctiva, Horner–Trantas dots around the limbus, and corneal shield ulcers.[4] Based on the primary site of involvement, VKC can present as limbal, tarsal, or mixed (both limbal and tarsal) forms.[5]

At present, the treatment of VKC aims at controlling ocular symptoms and avoiding the development of corneal complications. Traditional treatment methods include use of either single or a combination of antihistaminic (AH) and vasoconstrictor drugs, mast cell stabilizers, and nonsteroidal anti-inflammatory drugs (NSAIDs) having antiallergic effects. Other modern treatment modalities include cyclosporine, tacrolimus (TL), and mitomycin-C. Though steroids are potent antiallergic agents and used in severe stages, their prolonged use has a high risk for the development of complications like cataracts and glaucoma. The management of VKC is a challenge because of the lack of any consensual protocol and the need for frequent adjustments of medications according to the varying presentations from patient to patient.[6–12] Hence, the treatment of VKC should be personalized and tailored to the individual's need on the basis of disease severity.[13] Bonini et al.[4] proposed a therapeutic algorithm based on clinical severity grading to help physicians in the diagnosis and management of VKC patients. However, there is a disparity in the manifestations of VKC

Consultant, Department of Ophthalmology, Kar Vision Eye Hospital, Bhubaneswar, Odisha, [1]Senior Consultant, Department of Ophthalmology, RGH Rourkela, Odisha, [2]Prof & HOD, Department of Ophthalmology, VIMSAR, Burla, Sambalpur, Odisha, [3]Consultant, Department of Ophthalmology, Ruby Eye Hospital, Berhampur, Ganjam, Odisha, India

Correspondence to: Dr. Sabyasachi Pattanayak, 30 A, Bima Vihar, Sector 6, CDA, Cuttack, Odisha, India. E-mail: drspattanayak64@gmail.com

among Indian patients compared to our western counterparts, as environmental factors also play an important role in displaying the presentations among patients. Indian children have a longer contact time with environmental pollutants, making them more vulnerable to the profound manifestation of signs and symptoms of VKC.[14] Hence, a modification in the therapeutic algorithm is deemed necessary in our context for improving the efficacy of management. The present study was conducted to determine the safety and efficacy of a modified Bonini's therapeutic algorithm for different grades of VKC and prevention of its recurrence.

Methods

After obtaining approval from the institutional ethics review committee, the present prospective observational study was conducted from December 2013 to November 2015 in a tertiary eye care hospital in eastern India. As part of nonprobability sampling, 126 eyes of 63 clinically diagnosed consecutive patients of VKC, who consented to be part of the study and attended the ophthalmology Outpatient department (OPD) regularly for follow-ups, were included in this study. For calculation purposes, $n = 63$ (100%) was taken. The sample size was calculated based on the formula $n = Z^2pq/d^2$ for estimating proportions with a 95% confidence interval ($Z = 1.96$), absolute precision (d) of 10%, and proportion of recovery in the population (p) of 80%. Cases of VKC were defined as children and adolescents having complaints of chronic severe itching, redness, and watery eyes, with presence of papillary reaction either on the limbus or on palpebral conjunctiva.

Patients having asymmetric manifestations, bronchial asthma, inflammatory bowel disease, allergic rhinitis, and in addition, patients taking oral antiallergic drugs, immunosuppressants, and immunomodulators were excluded from the study. A standard clinical proforma was maintained in all cases, containing detailed medical history, systemic and ocular examination findings, including fluorescein staining, visual acuity using Snellen's visual acuity chart, laboratory investigations, and the final etiology. Details on disease severity, laterality, chronicity, history of atopy, and family history of VKC or associated allergic or atopic conditions and ocular signs and symptoms were noted on each visit.

Patients who presented with only one-eye involvement were considered as unilateral and the rest with involvement of both eyes as bilateral. VKC was called seasonal when patients presented with symptoms from March to July, and perennial when symptoms persisted throughout the year. The palpebral form included patients with characteristic signs of cobblestone papillae of >1 mm on the upper tarsal conjunctiva with no limbal infiltration, the limbal form included patients with limbal infiltration, and the mixed form had features of both palpebral and limbal types of VKC. The patients were graded based on the severity of the clinical picture in each visit and were administered the treatment protocol mentioned against that grade, as per Table 1.

For patients included in Grade 0, no treatment was given; in Grade 1, lubricating (LB) and AH drops were administered; Grade 2A patients received daily administration of LB drops and dual-action AH eye drops (olopatadine 0.1% twice daily); in Grade 2B, along with LB eye drops and dual-action (olopatadine 0.1%) eye drop, mast cell

Table 1: Clinical grading by Bonini *et al.* (from 0 to 5) and treatment protocol of VKC

VKC grading	Symptoms	Conjunctival hyperemia	Conjunctival secretion	Papillary reaction	Horner-Trantas dot	Corneal involvement	Treatment
Grade 0 (quiescent)	Absent	Absent/mild	Absent	Mild to moderate	Absent	Absent	No treatment
Grade 1 (mild intermittent)	Mild to occasional	Mild	Absent/mild	Mild to moderate	Absent	Absent	LB + AH
Grade 2A (moderate intermittent)	Mild to moderate intermittent	Mild	Mild	Mild to severe	Absent	Absent	LB + DA
Grade 2B (moderate persistent)	Mild to moderate persistent	Mild to moderate	Mild to moderate	Mild to severe	Absent	Superficial punctate keratitis may be present	LB + DA/MCS + NSAID
Grade 3 (severe)	Moderate to persistent severe	Moderate to severe	Moderate to severe	Moderate to severe with injection and swelling	Few Horner-Trantas dots may be present	Superficial punctate keratitis	LB + TS±CsA
Grade 4 (very severe)	Severe to persistent	Moderate to severe	Severe	Moderate to severe with injection and swelling	Numerous Horner-Trantas dots may be present	Corneal erosion or ulceration	LB + TL/SK
Grade 5 (evolution)	Absent or mild and occasional	Absent/mild	Absent	Mild to severe fibrosis	Absent	Absent	LB + TL/SK

AH=antihistaminic, CsA=cyclosporine A (0.05%), DA=dual-action (olopatadine 0.1%) eye drop, LB=lubricating drop, MCS=mast cell stabilizer, NSAID=nonsteroidal anti-inflammatory drug, SK=superficial keratectomy, TL=tacrolimus, TS=topical steroid, VKC=vernal keratoconjunctivitis

stabilizer and NSAID (ketorolac 0.4%) were added; in Grade 3, LB drops + topical steroids (TSs)/cyclosporin A (CsA) were given; and in Grade 4, LB drop + TL/superficial keratectomy (SK) were administered/performed, respectively. Contrary to the classical treatment algorithm by Bonini *et al.*,[5] we advised daily administration of LB and AH drops in Grade 1, the addition of NSAID (ketorolac 0.4%) in Grade 2B, and TL eye drop and SK in Grade 4 cases, whenever required. Though NSAIDs are not used commonly in allergic conjunctivitis, ketorolac 0.4% was added for a short term for cases not responding to AH drops alone, as it blocks the COX pathway and reduces inflammation, thus providing temporary relief from symptoms.[15,16]

The dosing pattern of LB, AH (naphazoline 0.056%, chlorpheniramine 0.01%), mast cell stabilizer (sodium cromoglycate 2%), and NSAID (ketorolac 0.4%) eye drops was one drop every 8 h. Dual-action AH (olopatadine 0.1%) eye drop was administered at one drop twice daily, TS (prednisolone acetate 1%) eye drop at one drop every 6 h for 1 week, and tapered eye drop at one drop per week for any acute and severe episode of the disease, whenever required. Cyclosporine (0.05%) eye drop was given as one drop twice daily for 6 months. Though TL, a calcineurin inhibitor that suppresses T-lymphocyte activation, was not included in the protocol, it was used as 0.03% eye ointment applied once at night only in refractory cases, considering its effectiveness as well as the most concerning adverse effect of risk of T cell lymphoma. SK was done in shield ulcer cases for rapid healing.

The patients were followed up every 2 weeks for 6 months, and subsequently up to 2 years if there were recurrences or aggravation of symptoms. Those patients who were upgraded to Grade 0 during follow-up examinations were advised to stop the treatment. Pretreatment recurrences were recorded from history using past medical records.

Statistical analysis

Data analysis was done following descriptive and inferential statistical procedures using IBM Statistical Package for the Social Sciences (SPSS) statistics version 24.0. Quantitative variables are presented as mean ± standard deviation (SD), and qualitative variables are presented as percentages. Categorical variables were classified following frequency procedures. The association of the clinical profile with Bonini's grading and the association of improvement of cases at different time points with treatment were studied using a cross-tabulation procedure and a Chi-squared test of independence. Comparison of Bonini's severity grading at different follow-ups with pretreatment grading and comparison of pre- and posttreatment recurrences were done using a nonparametric marginal homogeneity test. Cut-off value of $P < 0.05$ was considered to indicate statistical significance.

Results

The demographic characteristics of the study patients are listed in Table 2. A total of 63 patients diagnosed with VKC were included in the study. Of them, 48 (76.2%) were male and 15 (23.8%) were female with a male: female ratio of 3.2:1. The age range of the patients was 3–21 years, with a mean age of presentation of 8.8 ± 4.8 years. Only two (3.17%) patients were above the age of 20 years, whereas 61 (96.83%) patients were below the age of 20 years. The majority of patients belonged to the age group of 6–10 years (32, 50.8%), followed by an equal

Table 2: Demographic profile of cases

Variables	Classification	No.	%
Gender	Male	48	76.2
	Female	15	23.8
Age	Range	3-21 years	
	Mean±SD	8.85±4.48	
Age group in years	≤5	12	19
	6-10	32	50.8
	11-15	12	19
	16-20	5	07.8
	>20	2	3.4
VKC type	Palpebral	34	53.9
	Limbal	11	17.5
	Mixed	18	28.6
VKC course	Seasonal	55	87.3
	Perennial	08	12.7
VKC laterality	Unilateral	03	4.76
	Bilateral	60	95.24
Family history	Absent	57	90.5
	Present	6	9.5
	Total	63	100

SD=standard deviation, VKC=vernal keratoconjunctivitis

proportion of participants (12, 19.05%) in the age group of 0–5 and 11–15 years, respectively. A total of 34 (53.9%) cases had a palpebral form, 11 (17.5%) had a limbal form, and 18 (28.6%) had a mixed form of VKC. A total of 55 (87.3%) children had a seasonal pattern of presentation, whereas eight (12.7%) children had a perennial presentation. A total of 60 children (95.24%) had a bilateral presentation of symptoms and signs, whereas three (4.76%) children had a unilateral presentation. Only six (9.5%) children had a family history of atopy, whereas 57 (90.5%) children did not have any family history.

Itching was the most common symptom of presentation being observed in 60 (95.24%/120 eyes) children, followed by redness in 52 (82.54%/104 eyes), lacrimation in 45 (71.43%/90 eyes), and discharge in 42 (66.67%/84 eyes) children. The most common sign observed was tarsal papillae in 52 (82.54%) children, followed by lid edema in 39 (61.90%/78 eyes) children and Horner–Trantas dots in 12 (19.05%/24 eyes) children. Punctate keratopathy was observed in 29 (46.03%/58 eyes) children. The most common complication observed in the patients was conjunctivalization of the cornea in five (7.93%/10 eyes) patients, followed by shield ulcer in two (3.17%/4 eyes) and subepithelial deposits in one (1.58%/2 eyes) patient [Table 3].

According to severity, the patients were graded and distributed as per Table 4. A total of 26 (41.3%) patients belonged to Grade 2A, followed by Grade 2B, Grade 3, Grade 1, and Grade 4. The treatment given to the different grades of patients and the improvement of symptoms observed in those at 2-, 4-, and 6-week follow-ups were recorded. Also, the proportion of cases in different VKC classification grades posttreatment was observed at 6 weeks, 6 months, 12 months, and 24 months, as shown in Table 4.

At 6 weeks posttreatment, 44 (69.8%/88 eyes) cases improved to Grade 0 for which they were advised discontinuation of therapy and 11 (17.4%/22 eyes) cases improved to Grade 1,

that is, mild intermittent stage with cessation of treatment, except for an LB drop for maintenance. In comparison to pretreatment grading, the proportion of cases in grades 2A, 2B, 3, and 4 reduced significantly at 6 weeks ($P < 0.0001$). At 6 months posttreatment, 57 (90.5%/114 eyes) cases improved to Grade 0 and the proportion of cases in grades 1, 2A, 3, and 4 also improved significantly at 6 months ($P = 0.000$). At 24-month follow-up, in the posttreatment group, 87.3% of cases improved to Grade 0, which was significantly more compared to pretreatment cases (60%). But there was no significant difference in the proportion of grades between 6 and 12 months ($P = 0.166$) follow-up and between 12 and 24 months ($P = 0.405$) follow-up [Table 5].

Table 5 also shows the association of treatment protocols with outcomes at different time-points of follow-ups. At 6 weeks posttreatment, all the cases in Grade 1 improved to normal, but a total of 24 (92.3%/48 eyes) cases out of 26 in Grade 2A, 10 (58.8%/20 eyes) cases out of 17 in Grade 2B, two (22.2%/34 eyes) cases out of nine in Grade 3, and none out

of three in Grade 4 improved to normal. There was a significant association of improvement at 6 weeks with pretreatment grading ($P = 0.000$). At 6 months, the improvement was 100% in both grades 1 and 2A, 82.4% in Grade 2B, 77.8% in Grade 3, and 66.7% in Grade 4. There was no association of improvement at 6 months with pretreatment grading ($P = 0.074$). At 12 months, a significant association was found in the improvement status with pretreatment grading ($P = 0.002$). This is because one case in Grade 4, which had improved at 6 months, again slipped down to the same grade. At 24 months, there was no significant difference in the status of improvement among different gradings. The conclusion is that the improvement at 6 weeks was more pronounced in grades 1 and 2A. At subsequent periods, that is, 6, 12, and 24 months, the improvement in different grades with respect to pretreatment grading was found to be homogenous. This implies that the cases in grades 1 and 2A improved faster than the cases in the higher severity grade.

Comparing the pretreatment and posttreatment recurrences, at the pretreatment level, in 30 (47.6%/60 eyes) cases, there was recurrence and in 33 (52.4%/66 eyes) cases, there was no recurrence. Out of the 30 cases with a history of recurrence, in 21 cases, there was only one recurrence, two recurrences in four cases, three recurrences in two cases, and four, five, and six recurrences in one case each. Posttreatment, there were recurrences only in 14 (22.2%/28 eyes) cases, while there was no recurrence in 49 (77.8%/58 eyes) cases. Posttreatment, two or more recurrences were observed only in three (4.8%/6 eyes) cases compared to nine (14.3%/18 eyes) cases in the pretreatment period. There was also a significant reduction in the number of recurrences in the posttreatment ($P = 0.001$) period [Table 6].

Table 7 analyzes the association between recurrence and nonrecurrence with Bonini grading at pretreatment and posttreatment separately. In both cases, it was found that the number of recurrences significantly decreased in all grades. However, recurrence rates were higher in Grade 3 (77.8%) and Grade 4 (33.3%) compared to Grade 1 (100%) and Grade 2 (92.3%).

Discussion

Treatment protocols of VKC vary from physician to physician for the same severity of condition because of the lack of definitive management protocols in the existing literature.[10]

Table 3: Initial clinical profile of cases (*N*=63) along with associated complications

Variables	Response			
	Present		Absent	
	No.	%	No.	%
Itching	60	95.24	3	4.76
Congestion	52	82.5	11	17.5
Discharge	42	66.7	21	33.3
Papillae	42	66.7	21	33.3
Lid edema	39	61.9	24	38.1
Horner-Trantas spots	12	19	51	81
Conjunctivalization	6	9.5	57	90.5
Superficial punctate Keratitis	29	46	34	54
Shield ulcer	2	3.2	61	96.8
Subepithelial deposit	1	1.6	62	98.4
Associated complications				
Subepithelial deposits	1 (1.58%)			
Shield ulcer	2 (3.17%)			
Conjunctivalization of cornea	5 (7.93%)			

Table 4: Distribution of cases as per Bonini grading with treatment protocol and improvement of grading category over a period of 2 years

Classification	Bonini grading		6 weeks		6 months		12 months		24 months	
	No.	%	No.	%	No.	%	No.	%	No.	%
Normal	0	0	44	69.8	57	90.5	58	92.1	55	87.3
1 (LB + AH)	8	12.7	11	17.5	2	3.2	4	6.3	6	9.5
2A (LB + DA)	26	41.3	3	4.8	2	3.2	0	0	2	3.2
2B (LB + DA/MCS + NSAID)	17	27	1	1.6	2	3.2	1	1.6	0	0
3 (LB + TS±CsA)	9	14.3	3	4.8	0	0	0	0	0	0
4 (LB + TL/SK)	3	4.8	1	1.6	0	0	0	0	0	0
Total	63	100	63	100	63	100	63	100	63	100

AH=antihistaminic, CsA=cyclosporine A (0.05%), DA=dual-action antihistaminic, LB=lubricating agent, MCS=mast cell stabilizer, NSAID=nonsteroidal anti-inflammatory drug, SK=superficial keratectomy, TL=tacrolimus, TS=topical steroid. Marginal homogeneity test *P* value: Bonini grading versus 6 weeks=0.000; 6 weeks versus 6 months=0.000; 6 months versus 12 months=0.166; 12 months versus 24 months=0.405; Bonini grading versus 24 months=0.000

Table 5: Association of treatment protocol with outcomes at different follow-ups

Bonini grading	Different time-points of follow-ups							
	6 months		12 months		12 months		24 months	
	No improvement	Improvement	No improvement	Improvement	No improvement	Improvement	No improvement	Improvement
	n (%)		n (%)		n (%)		n (%)	
1 (n=8)	0 (0%)	8 (100%)	0 (0%)	8 (100%)	0 (0%)	8 (100%)	0 (0%)	8 (100%)
2A (n=26)	2 (7.7%)	24 (92.3%)	0 (0%)	26 (100%)	0 (0%)	26 (100%)	1 (3.8%)	25 (96.2%)
2B (n=17)	7 (41.2%)	10 (58.8%)	3 (17.6%)	14 (82.4%)	2 (11.8%)	15 (88.2%)	5 (29.4%)	12 (70.6%)
3 (n=9)	7 (77.8%)	2 (22.2%)	2 (22.2%)	7 (77.8%)	1 (11.1%)	8 (88.9%)	2 (22.2%)	7 (77.8%)
4 (n=3)	3 (100%)	0 (0%)	1 (33.3%)	2 (66.7%)	2 (66.7%)	1 (33.3%)	0 (0%)	3 (100%)
Total	19 (30.2%)	44 (69.8%)	6 (9.5%)	57 (90.5%)	5 (7.9%)	58 (92.1%)	8 (12.7%)	55 (87.3%)
χ^2, P	27.301 (0.000)		8.539 (0.074)		17.558 (0.002)		8.458 (0.076)	

Table 6: Comparison of pre- and posttreatment number of recurrences

Number of recurrences	Pretreatment recurrence		Posttreatment recurrence		Marginal homogeneity test P
	No.	%	No.	%	
No recurrence	33	52.4	49	77.8	0.001
1	21	33.3	11	17.5	
2	4	6.3	3	4.8	
3	2	3.2	0	0	
4	1	1.6	0	0	
5	1	1.6	0	0	
6	1	1.6	0	0	
Total	63	100	63	100	

Hence, we performed our study to analyze the efficacy of the Bonini's grading system and a slightly modified treatment algorithm for VKC, as grading of VKC is critical for analyzing the response following the management.

Our study, like Bonini et al.,[4] also showed a significant gender disparity with skewing toward male children, who were three times more commonly affected compared to females. But Leonardi et al.[17] observed a male-to-female ratio of 3.3:3.5. Most of the studies reported in the literature have male dominance over females,[18] which is attributed to increased outdoor activities of male children that lead to accentuated exposure to allergens.

Age plays a critical role in the manifestation of symptoms in VKC.[19] Children in the age group of 5–10 years have a higher risk of onset, and our study showed that 50.8% of children affected were in the age group of 6–10 years.[20] However, children <5 years and >10 years of age also have the risk of developing allergic conjunctivitis, but the risk of onset is significantly reduced after 16 years of age.[21]

The palpebral variant is the most common type of manifestation.[22] Papillae in the palpebral conjunctiva help in grading the VKC.[23] The density of papillae is directly proportional to the manifestation of symptoms.[24] An irregular palpebral surface leads to the instability of the tear film, eventually causing ocular discomfort.[25] Hence, response to

treatment is gauged by the reduction in the intensity of papillae. Our study witnessed that 99% of cases had a significant reduction in the papillae following treatment.

We observed that 87% of cases had seasonal exacerbations of the condition and 13% of the cases had a chronic perennial form. Seasonal exacerbations are attributed to the changing environmental allergens and pollutants in different seasons.[26] The spring season has the highest onset and aggravation of symptoms owing to enormous increase in suspended particles in the atmosphere.[27] Saboo et al.[14] reported that 68% of 468 cases studied had seasonal exacerbations. Leonardi et al.,[28] in their meta-analytic study, also observed a high incidence of allergic conjunctivitis compared to perennial allergy.

Itching is the most common manifestation observed in our study. Azari et al.,[29] in their update on conjunctivitis, had created an algorithm in which itching of eyes was the most associated symptom with ocular allergy. A patient with watering and discharge in addition to itching rules in favor of allergic conjunctivitis, and its absence refers to its infective component.[29]

A total of eight (12%) cases witnessed corneal complications, which marked the adverse impact of limbal and palpebral papillae, and seven cases (8%) showed loss of limbal stem cells, leading to abnormal growth of conjunctival vessels over the cornea [Table 3]. Limbal stem cell loss is attributed to the limbal papillae coaxing to a continuous process of inflammation over the limbus slowly annexing the stem cells.[30] Two cases had a significant shield ulcer over the superior aspect of cornea because of dense papillae over the palpebral surface culminating to an irregular tear film, which, eventually, makes the corneal epithelium unhealthy. An unhealthy corneal epithelium is at a higher risk of breach in its continuity, spawning shield ulcer.[31]

The grading and management of VKC is essential to analyze the efficacy of the treatment and to avoid any complications arising out from misuse of TSs. Multiple grading systems are available in literature, which are either based on symptoms or based on clinical signs or a combination of both signs and symptoms. Pucci et al.[32] graded VKC based on ocular symptoms in the range 0–15. Spadavecchia et al.[33] developed a grading system based on the classical signs of allergic conjunctivitis, including conjunctival hyperemia, papillae, and

Table 7: Association between pre- and posttreatment recurrences with Bonini grading

Treatment recurrence	Status	Bonini grading					Total	P
		1	2A	2B	3	4		
				n (%)			*n* (%)	
Pretreatment	No recurrence	8 (100%)	16 (61.5%)	8 (47.1%)	0 (0%)	1 (33.3%)	33 (52.4%)	
	Recurrence	0 (0%)	10 (38.5%)	9 (52.9%)	9 (100%)	2 (66.7%)	30 (47.6%)	0.001
Posttreatment	No recurrence	8 (100%)	24 (92.3%)	13 (82.9%)	7 (77.8%)	1 (33.3%)	49 (77.8%)	
	Recurrence	0 (0%)	2 (7.7%)	4 (17.1%)	2 (22.2%)	2 (66.7%)	14 (22.2%)	0.005
	Total	8 (100%)	26 (100%)	17 (100%)	9 (100%)	3 (100%)	63 (100%)	

Horner–Trantas spots. However, the grading created by Bonini *et al.*[34] is an amalgamation of classical symptoms and signs of VKC. It has six grades starting from Grade 0 to Grade 5. Signs and symptoms are in ascending order from Grade 0 to Grade 4, followed by Grade 5, which is the stage of evolution, and there is complete redressal of symptoms with the development of conjunctival scar. Our study incorporated the Bonini *et al.*[5] grading system and created a management protocol based on the grade of VKC. We observed that 70% of patients reached Grade 0 by the end of 6 weeks and 90% by the end of 6 months following the modified management protocol. Grade 0 was considered as the end point of management.

Lower grades of VKC were more responsive to management compared to higher grades. We observed 100% of cases in grades 1 and 2 had improved to Grade 0. Patients with higher grades were more refractory to treatment and required a longer time for improvement. Chatterjee *et al.*[35] also showed an increased incidence of resistance to treatment in higher grades of VKC, which needed additional TL for the regression of papillae. Ueta *et al.*[36] had to add rebamipide to the conventional treatment for patients with Grade 4 VKC. However, we witnessed a definitive improvement in Grade 3 and Grade 4 VKC following our protocol, but it took longer to respond to the treatment and there was regression of papillae at the end of 6 months. It is well established in literature that patients with higher grades require therapy for a longer duration compared to those with lower grades.[37]

Recurrent VKC is commonly seen in children and young individuals.[38] It is due to the waxing and waning of the innate immune system of the ocular surface compounded by the seasonal aggravation of allergens in the atmosphere. We observed a significant reduction in the incidence of recurrences following the treatment protocol, with a *P* value <0.001. In management, a reduction in recurrence is critical for improvement. Recurrences lead to a degraded ocular surface adversely affecting the quality of vision in the future.[39] With a reduction in recurrence, there is a decrease in sensitivity to light and wind and an improvement in the quality of the tear film.

Our therapeutic algorithm showed a significant decrease in the proportion of patients with symptomatic allergic conjunctivitis and also prevention of recurrences. Our study showed >90% improvement in the lower grades (grades 1 and 2) and 80% improvement in higher grades (grades 3 and 4). However, Bonini *et al.*[40] did not validate the efficacy of the proposed grading system; hence, this is the first study, to the best of our knowledge, validating the success of management based on adherence to the treatment protocol

proposed. Leonardi *et al.*[41] reported a 68% reduction in the recurrences posttreatment in 12 months, and our study showed a 78% reduction in the recurrences over 24 months.

Conclusion

The modified Bonini's treatment protocol used in this study is found to be effective in managing VKC of all severity grades by shortening the duration of treatment, preventing recurrences, and minimizing the number of visits to the clinic, but a long-term study with a larger sample size will better establish the effectiveness of the treatment protocol.

Financial support and sponsorship
Nil.

Conflict of interest
There are no conflicts of interest.

References

1. Vichyanond P, Pacharn P, Pleyer U, Leonardi A. Vernal keratoconjunctivitis: A severe allergic eye disease with remodeling changes. Pediatr Allergy Immunol 2014. doi: 10.1111/pai. 12197.

2. Heinz C, Heiligenhaus A. Keratoconjunctivitis vernalis [Vernal keratoconjunctivitis]. Klin Monbl Augenheilkd 2014;231:505-11. German.

3. Bielory L. Allergic and immunologic disorders of the eye. Part II: Ocular allergy. J Allergy Clin Immunol 2000;106:1019–32.

4. Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, *et al*. Vernal keratoconjunctivitis revisited. Ophthalmology 2000;107:1157–63.

5. Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. Curr Opin Allergy Clin Immunol 2007;7:436–41.

6. Leonardi A, Busca F, Motterle L, Cavarzeran F, Fregona IA, Plebani M, *et al*. Case series of 406 vernal keratoconjunctivitis patients: A demographic and epidemiological study. Acta Ophthalmol Scand 2006;84:406–10.

7. Di Zazzo A, Bonini S, Fernandes M. Adult vernal keratoconjunctivitis. Curr Opin Allergy Clin Immunol 2020;20:501-6.

8. Lambiase A, Minchiotti S, Leonardi A, Secchi A, Rolando M, Calabria G, *et al*. Prospective, multicenter demographic and epidemiological study on vernal keratoconjunctivitis: A glimpse of ocular surface in Italian population. Ophthalmic Epidemiol 2009;16:38-41.

9. Tabbara KF. Ocular complications of vernal keratoconjunctivitis. Can J Ophthalmol 1999;34:88–92.

10. Leonardi A. Vernal keratoconjunctivitis: Pathogenesis and treatment. Prog Retin Eye Res 2002;21:319–39.

11. Leonardi A, Secchi AG. Vernal Keratoconjunctivitis. Int Ophthalmol

Clin 2003;43:41–58.

12. Addis H, Jeng BH. Vernal keratoconjunctivitis. Clin Ophthalmol 2018;12:119–23.

13. Mantelli F, Santos MS, Petitti T, Sgrulletta R, Cortes M, Lambiase A, *et al*. Systematic review and meta-analysis of randomised clinical trials on topical treatments for vernal keratoconjunctivitis. Br J Ophthalmol 2007;91:1656–61.

14. Saboo US, Jain M, Reddy JC, Sangwan VS. Demographic and clinical profile of vernal keratoconjunctivitis at a tertiary eye care center in India. Indian J Ophthalmol 2013;61:486-9.

15. Sharma A, Gupta R, Ram J, Gupta A. Topical ketorolac 0.5% solution for the treatment of vernal keratoconjunctivitis. Indian J Ophthalmol 1997;45:177–80.

16. Leonardi A. Management of vernalkeratoconjunctivitis. Ophthalmol Ther. 2013;2:73-88. doi:10.1007/s40123-013-0019-y.

17. Leonardi A, Busca F, Motterle L, Cavarzeran F, Fregona IA, Plebani M, *et al*. Case series of 406 vernal keratoconjunctivitis patients: A demographic and epidemiological study. Acta Ophthalmol Scand 2006;84:406–10.

18. Brody JM, Foster CS. Vernal conjunctivitis. In: Pepose JS, Holland GN, Wilhelmus KR, editors. Ocular Infection and Immunity, Chap. 27. Mosby: St Louis; 1996.

19. Akinsola FB, Sonuga AT, Aribaba OT, Onakoya AO, Adefule-Ositelu AO. Vernal keratoconjunctivitis at Guinness Eye Centre, Luth (a five year study). Nig Q J Hosp Med 2008;18:1–4.

20. Addis H, Jeng BH. Vernal keratoconjunctivitis. Clin Ophthalmol 2018;12:119-23.

21. Sofi RA, Mufti A. Vernal Keratoconjunctivitis in Kashmir: A temperate zone. Int Ophthalmol 2016;36:875-9.

22. Sacchetti M, Plateroti R, Bruscolini A, Giustolisi R, Marenco M. Understanding vernal keratoconjunctivitis: Beyond allergic mechanisms. Life (Basel) 2021;11:1012.

23. Kosrirukvongs P, Vichyanond P, Wongsawad W. Vernal keratoconjunctivitis in Thailand. Asian Pac J Allergy Immunol 2003;21:25-30.

24. Zicari AM, Capata G, Nebbioso M, De Castro G, Midulla F, Leonardi L, *et al*. Vernal Keratoconjunctivitis: An update focused on clinical grading system. Ital J Pediatr 2019;45:64.

25. Le Q, Hong J, Zhu W, Sun X, Xu J. *In vivo* laser scanning confocal microscopy of vernal keratoconjunctivitis. Clin Exp Ophthalmol 2011;39:53-60.

26. Hom MM, Nguyen AL, Bielory L. Allergic conjunctivitis and dry eye syndrome. Ann Allergy Asthma Immunol 2012;108:163-6.

27. Schröder K, Finis D, Meller S, Wagenmann M, Geerling G, Pleyer U. Saisonale allergische Konjunktivitis [Seasonal allergic conjunctivitis]. Ophthalmologe 2017;114:1053-65. German.

28. Leonardi A, Piliego F, Castegnaro A, Lazzarini D, La Gloria Valerio A, Mattana P, *et al*. Allergic conjunctivitis: A cross-sectional study. Clin Exp Allergy 2015;45:1118-25.

29. Azari AA, Barney NP. Conjunctivitis: A systematic review of diagnosis and treatment. JAMA 2013;310:1721-9.

30. Le Q, Xu J, Deng SX. The diagnosis of limbal stem cell deficiency. Ocul Surf 2018;16:58-69.

31. Solomon A. Corneal complications of vernal keratoconjunctivitis. Curr Opin Allergy Clin Immunol 2015;15:489-94.

32. Pucci N, Novembre E, Cianferoni A, Lombardi E, Bernardini R, Caputo R, *et al*. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. Ann Allergy Asthma Immunol 2002;89:298-303.

33. Spadavecchia L, Fanelli P, Tesse R, Rizzo G, Procoli U, Bellizzi M, *et al*. Prognosi e trattamento della cheratocongiuntivite Vernal in età pediatricia: Studio pilota su 197 pazienti [Prognosis and treatment of Vernal keratoconjunctivitis in pediatric age: pilot study on 197 patients]. Minerva Pediatr 2010;62:239-44. Italian.

34. Bonini S, Sacchetti M, Mantelli F, Lambiase A. Clinical grading of vernal keratoconjunctivitis. Curr Opin Allergy Clin Immunol 2007;7:436-41.

35. Chatterjee S, Agrawal D. Tacrolimus in corticosteroid-refractory vernal keratoconjunctivitis. Cornea 2016;35:1444-8.

36. Ueta M, Sotozono C, Koga A, Yokoi N, Kinoshita S. Usefulness of a new therapy using rebamipide eyedrops in patients with VKC/AKC refractory to conventional anti-allergic treatments. Allergol Int 2014;63:75-81.

37. Singhal D, Sahay P, Maharana PK, Raj N, Sharma N, Titiyal JS. Vernal keratoconjunctivitis. Surv Ophthalmol 2019;64:289-311.

38. De Smedt S, Wildner G, Kestelyn P. Vernal keratoconjunctivitis: An update. Br J Ophthalmol 2013;97:9-14.

39. Wong AH, Barg SS, Leung AK. Seasonal and perennial allergic conjunctivitis. Recent Pat Inflamm Allergy Drug Discov 2014;8:139-53.

40. Bonini S, Coassin M, Aronni S, Lambiase A. Vernal keratoconjunctivitis. Eye (Lond) 2004;18:345-51.

41. Leonardi A, Piliego F, Castegnaro A, Lazzarini D, La Gloria Valerio A, Mattana P, *et al*. Allergic conjunctivitis: A cross-sectional study. Clin Exp Allergy 2015;45:1118-25.