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Vernal Keratoconjunctivitis in Thailand

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SUMMARY **A prospective, cross-sectional and randomized cross-over study was conducted to study the clinical features and treatment outcome among Thai patients with vernal keratoconjunctivitis (VKC). History-taking and eye examinations were performed. Mild cases of VKC were given topical antihistamine four times daily. Moderate and severe cases of VKC were treated with topical lodoxamide four times a day. Severe cases of VKC were given topical corticosteroids. Moderate and severe cases of VKC, which were refractory to treatment with either corticosteroids or a mast cell stabilizer had topical cyclosporine 0.5 % instilled four times daily. Five patients were exposed to two different treatment regimens in sequence. As main outcome measures, itching, foreign body sensation, photophobia, conjunctival injection, papillae and chemosis were evaluated weekly. The patients with the palpebral type of VKC had daily symptoms, which were more severe and triggered by house-dust with a significant difference among the groups. Limbal VKC was associated with allergic rhinitis more commonly than palpebral VKC. Positive results of skin prick testing to acacia, careless weed, mold, Johnson grass and cow's milk were significantly more common in patients with palpebral VKC. The most common symptoms and signs were found in the mixed type of VKC. Purulent discharge, pannus and lid erythema were found in the palpebral type. Levocabastine hydrochloride was sufficient for mild cases of limbal VKC; lodoxamide for the limbal and mixed types. Prednisolone acetate was the drug of choice in severe cases of any type but only for a short period of time. The success rate of topical cyclosporine in the palpebral type was lower than in the limbal type due to an intolerable burning sensation. Topical cyclosporine used in 4 patients with limbal and palpebral type had a success rate of 100% which was greater than in the lodoxamide group (66.7%, 0%). Compared with topical corticosteroid-treated eyes in one patient, the success rate in topical cyclosporine-treated eyes was not success. Grading the severity of each type of VKC is crucial to obtain good response of any medication and compliance. Topical cyclosporine 0.5% can be an alternative drug to relieve symptoms and signs of VKC in order to avoid steroid-induced glaucoma.**

Vernal keratoconjunctivitis (VKC) is a severe type of allergic conjunctivitis causing disturbance of normal activities at school or work due to severe itching, foreign body sensation, difficulty in opening the eyelids, photophobia and a copious mucous discharge.[1] These symptoms can persist for weeks if not treated appropriately. Three types of VKC are recognized, including the limbal type (fine papillae with limbal infiltration, Horner-Trantas dot), the palpebral type with giant papillae (more than 1 mm) and a mixed type.[2] The reasons underlying the development of the various types of VKC in these patients are poorly studied and little understood. Risk factors include age, underlying atopic predisposition, extent of allergen exposure and individual immune response to antigenic stimulation. Despite appropriate management and environmental control, varying responses to the same medication have been observed.

Therapy for mild VKC includes preservative-free artificial tears, cold compresses and antihistamines. Treatment in severe cases of VKC is still problematic due to frequent exacerbations. Topical corticosteroids are usually given only for a short period of time to avoid the risk of side effects including glaucoma and infection.[3] Mast cell stabilizers, such as topical lodoxamide can prevent attacks but need to be taken for a few weeks to ob-

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tain the maximum response.[4-5] The non-steroidal immunomodulating agent, cyclosporine (2% topical), which is used in the prevention of corneal graft rejection, uveitis, and anterior segment inflammation appears to be safe and effective in the treatment of severe VKC.[6-9]

The purpose of this study was to evaluate the clinical profiles of various types of VKC including treatment and adverse reactions.

MATERIALS AND METHODS

Forty-eight patients with vernal keratoconjunctivitis diagnosed by recurrent severe itching, foreign body sensation or ropy discharge associated with atopic disease were studied prospectively at Siriraj Hospital from March 1998 to December 2001. Inclusion criteria were recurrent bilateral symptomatic VKC before entry into the study. The patients had to stop all previous medications for at least 1 week as a washout period before eye examination for evaluation and grading of symptoms and signs of allergic conjunctivitis as in Table 1, modified from Bonini's report.[10] Classification into mild, moderate and severe cases was performed according to these criteria. Informed consent was obtained from the parents or the patient if aged over 18 years. The exclusion criteria were bacterial conjunctivitis, viral conjunctivitis or toxic conjunctivitis. Patients with associated eye or systemic diseases or taking oral antileukotriene or corticosteroid were excluded, except for oral antihistamine.

Patient managements

One patient with a mild case of VKC was given an H1 antagonist , levocabastine hydrochloride, twice daily for a week. Eight patients with mild to moderately severe VKC were given lodoxamide four times a day for at least one month, but 3 patients were lost to follow up. Ten patients with severe VKC were prescribed topical 1% prednisolone acetate four times a day until improvement was noted or for a maximum period of two weeks. If an increase in intraocular

Table 1 Grading of the severity of symptoms and signs of VKC used in the study.

Symptoms & signs	1 = mild	2 = moderate	3 = severe
Itching	Occasionally	Frequently, tolerable rub eye	Rubs eye all day
Foreign body sensation	Occasionally	Frequently	All day
Tearing	Occasionally	Frequently	All day
Photophobia	Occasionally	Eye(s) sometimes closed	Eye(s) frequently closed
Discharge	Occasionally	Frequently	All day
Mucous discharge	Occasionally	Few strand	Easily detectable
Burning	Occasionally	Frequently	All day
Swollen eyelid	Feels full in morning	All day	Interpalpebral fissure decreased
Chemosis	Conjunctiva separated from sclera	Raised conjunctiva	Ballooning of conjunctiva
Conjunctival injection (red eye)	Minimal	Obvious	Diffuse redness
Papillae size	< 0.2 mm.	0.2 – 0.9 mm.	≥ 1 mm
Giant papillae size, area	1-1.9 mm, < 25%	2-5 mm, 25-50%	> 5 mm, > 50 %
Superficial pannus	1 quadrant	2 quadrants	≥ 3 quadrants
Punctated epitheliopathy	< 1/2 cornea	> 1/2 cornea	Confluent with mucous plaque and ulcer
Shield ulcer	Transparent base	White deposit	Elevated plaque
Limbal infiltrate	Mild prominent limbal vessel	Moderate area	Severe with pannus 360°
Horner Trantas dot	1 quadrant	2 quadrants	≥ 3 quadrants
Visual acuity	6/9 – 6/12	6/18 – 6/36	≤ 6/60

pressure was detected, the medication was stopped. Twenty-four patients with VKC of moderate severity and severe cases of VKC refractory to corticosteroids and mast cell stabilizers were treated with 0.5% topical cyclosporine four times daily, with 2 patients lost to follow-up. Three patients in this group (12.5%) had a history of steroid induced glaucoma with uncontrollable and advanced optic nerve damage as a result of steroid overuse.

A randomized cross-over study was conducted in 5 cooperating patients who could visit weekly for 2 months. Four patients were treated with 0.5% topical cyclosporine four times a day for one month which was compared to lodoxamide hydrochloride four times a day for one month with one week washout period before starting the alternative drug. One patient was treated with topical cyclosporine 0.5% for two weeks which was compared to 1% prednisolone acetate four times daily for 2 weeks.

All patients were given the following treatments; cold compresses with preservative-free artificial tears every hour until bedtime, protection of the eye from the light and wind using sunglasses and the patients were instructed not to rub their eyes. For patients with a shield ulcer or suspected superimposed bacterial infection, topical antibiotics were given four times a day until the ulcer was healed. The main outcome measures were a decrease in symptoms and signs at 1 week and toleration of medication. This was defined as success. The need for additional medication in order to control inflammation within 2 weeks was defined as failure.

Discontinuous variables were analyzed by Wilcoxon's rank sum test for each variable; and continuous variables were analyzed by ANOVA.

RESULTS

Among forty-eight patients with VKC were 28 with the limbal type (58.3%), 16 with the palpebral type (33.3%) and 4 with the mixed type (8.3%). Mean age ± SD at presentation was 9.6 ± 5.0 years (range 4-29 years) with a male preponderance (81%). Ninety-two per-

Table 2 Significant characteristics in each type of VKC

	%			*p* - value
	Limbal (n = 28)	Palpebral (n = 16)	Mixed (n = 4)	
Mean age (yrs ± SD)	9.9 ± 5.6	9.9 ± 4.4	7.2 ± 1.2	0.291
Mean duration (yrs ± SD)	3.4 ± 3.6	3.5 ± 3.5	0.4 ± 0.2	0.117
Allergic rhinitis in family	52.4	83.3	100	0.013
Frequency of symptoms				0.017
Every day	21.4	65.6	25.0	
Every week	25.0	-	25.0	
Every month	35.7	34.4	50.0	
Others	18.0	—	—	
Severity				0.006
Mild	21.4	6.3	—	
Moderate	32.1	12.5	—	
Severe	46.4	81.3	100	
Symptoms in the evening	67.9	31.3	75.0	0.002
Season				0.043
All year	71.4	75.0	25.0	
Summer	14.3	18.8	50.0	
Other	14.3	6.3	25.0	
Trigger: House-dust	78.6	93.3	50.0	0.017
Dog , cat	3.7	-	25.0	0.008
Associated disease				
Allergic rhinitis	88.9	75.0	50.0	0.019

cent of the patients were students. Sixty-nine percent had a family history of atopy such as allergic rhinitis (65.7%), asthma (28.6%), urticaria (8.6%), atopic dermatitis (5.7%) or conjunctivitis (5.7%). A family history of allergic rhinitis was found statistically more frequently in those with the mixed type of VKC (p = 0.013, Table 2). Age of onset varied from 1 to 15 years with an average ± SD of 6.2 ± 3.1 years. The average duration of symptoms (although intermittent) before the study for all types of VKC was 3.2 ± 3.5 years, but those with mixed type VKC had a statistically shorter duration of symptoms (4.7 ± 2.7 months) compared to other types of VKC (p < 0.001). Most patients with the palpebral type had daily symptoms whereas those with other types of VKC had monthly symptoms. Many patients had symptoms throughout the year (69%), those with the mixed type of VKC having more symptoms in the summer. Severe symptoms (all types) were found in 62% of the patients. The precipitating factors (triggers) in all patients were house-dust (81%) and hot weather (43%). Pets were found to trigger symptoms in those with limbal or mixed VKC. Symptoms occurred in the evening in 56%, at night in 52%, in the afternoon in 42% and in the morning in 37%. Eighty-one percent of the patients had associated allergic diseases; (allergic rhinitis 81% - mostly in limbal type, asthma 11%, atopic dermatitis 13%). Forty-two percent had had successful treatment. Topical cyclosporine (0.5%) had a success rate of 75%, corticosteroids 43%, mast cell stabilizers 38% and antihistamines 25%.

Eighty-one percent of the patients with VKC had had skin prick testing performed, with positive results in 67%. Positive skin testing was found to house-dust mite (56%), house-dust (31%), Johnson grass (26%), cockroach 26%, food 26% (mainly to shrimp, most commonly found in the mixed type of VKC), cat 19%, fungus 16% (mostly found in the palpebral type), kapok 16%, careless weed 14% (especially in palpebral type), and dog 8% (Table 3). Conjunctival scraping in patients with VKC were performed in 28%, with eosinophils found in 66.7%.

Symptoms in patients with VKC included itching (75%), swollen eyelids (69%) (mostly found in the mixed type), tearing (64%), red eye (62%), foreign body sensation (61%) and mucous discharge (60%) (mostly found in the mixed type), and photophobia (58%) (mostly found in the palpebral type) (Table 4). The most common signs in patients with VKC were chemosis and fine papillae (93%), Horner-Trantas dot (46%), limbal infiltrates (limbitis) (41%), giant papillae (37%), corneal epitheliopathy (22%) (mostly found in the mixed type), blepharitis (20%) and shield ulcers without epithelial or mucous plaques in only 2%. Severe visual impairment was found in only 3%. The intraocular pressure was higher than 20 mm Hg in 2 patients at 24 and 42 mm Hg, respectively.

The H1 antagonist levocabastine hydrochloride relieved symptoms and signs successfully in those with mildly severe limbal type VKC as shown in Table 5. Treatment with lodoxamide in those with mild to moderately severe VKC was successful. Prednisolone acetate was successful within a week in severe cases. However, steroid induced glaucoma occurred in 1 out of 8 patients (12.5%) after about two weeks of medication. Treatment failure occurred in the 0.5% of the cyclosporine group in those with moderate and severe VKC (4 out of 22 patients [18%]). Treatment failure was often due to poor compliance because of an intolerable burning sensation after application of the drug (0.5% cyclosporine).

In the randomized crossover study between cyclosporine and lodoxamide, cyclosporine was found to have a higher efficacy than lodoxamide. In comparison bet-

Table 3 Significant differences in positive results of skin prick testing for each type of VKC

	%			p - value
	Limbal	Palpebral	Mixed	
Acacia	-	33.3	-	0.001
Careless weed	5.3	30.8	-	0.010
Penicillium		23.1	-	0.003
Cladosporium	-	15.4	-	0.017
Johnson grass	-	15.4	-	0.015
Cow's milk	-	16.7	-	0.024
Shrimp	10	8.3	50	0.049

Table 4 Symptoms and signs in patients with VKC

	%			*p* - value
	Limbal	Palpebral	Mixed	
Foreign body sensation	55.6	69.2	75.0	0.004
Mucous discharge	50.0	66.7	100.0	0.018
Photophobia	44.4	80.8	75.0	0.020
Purulent discharge	27.8	46.2	-	0.026
Nasal symptoms	42.6	73.9	25.0	0.041
Small papillae	100.0	81.8	75.0	< 0.001
Lid swelling	62.5	75.0	100.0	0.014
Horner-Trantas dot	61.1	4.2	75.0	< 0.001
Superficial punctate-keratitis (epitheliopathy)	33.3	54.2	62.5	0.030
Limbitis	50.0	-	75.0	0.002
Giant papillae (> 1 mm)	7.4	91.7	75.0	< 0.001
Pannus	9.3	30.0	-	0.034
Lid erythema	7.4	33.3	-	0.011

Table 5 Treatment in each type of VKC

Drug	Limbal	Palpebral	Mixed
H1 antagonist (levocabastine)	1	-	-
Success	1 (100%)	-	-
Iodoxamide	5	2	1
Lost to follow - up	2 (40%)	1 (50%)	-
Success	3/3 (100%)	0/1 (0%)	1/1 (100%)
Corticosteroid (prednisolone acetate 1%)	6	3	1
Lost to follow - up	2 (33.3%)	-	-
Success	4/4 (100%)	3/3 (100%)	1/1 (100%)
0.5 % cyclosporine	12	10	2
Lost to follow - up	1 (8.3%)	1 (10%)	-
Success	9/11 (81.8%)	7/9 (77.8%)	2/2 (100%)
Cyclosporine VS	3/3 (100%)	1/1 (100%)	-
Lodoxamide	2/3 (66.7%)	0/1 (0%)	-
Success			
Cyclosporine VS	0/1 (0%)	-	-
Corticosteroid	1/1 (100 %)	-	-
Success			

ween cyclosporine and corticosteroid, the success rate with corticosteroid was better than with cyclosporine, though perhaps due to a premature cessation of cyclosporine because of intolerable burning sensation (Table 5).

DISCUSSION

The most common clinical type of VKC in this study was the limbal type as has been reported in other countries with a hot climate.[3] Atopy with allergic rhinitis was commonly found in the mixed type which was significantly different from the other types. However, there were only few patients with mixed type VKC. Some patients with the limbal type may turn into mixed type if the disease progresses. Patients with palpebral VKC had more severe symptoms than the other types perhaps due to irritation caused by the giant papillae. A subjective history of contact with allergens that appear to produce symptoms is very useful and can help to advice appropriate avoidance as part of the overall management resulting in a reduction in the severity of symptoms. A variety of unavoidable allergens in the palpebral type of VKC may aggravate symptoms and thus make this group more likely to have severe disease. Because of their detrimental effects, shield ulcers and scars should be treated immediately in order to preserve vision. Topical corticosteroids produce the best clinical response in severe cases but can only be used for a short period of time in order to avoid steroid induced glaucoma. Therefore, an alternative choice of drug in the management of VKC should be topical cyclosporine as reported by others.[6-9]

Lodoxamide, an H1 antagonist, or a combination of all mentioned drugs can be used to decrease the frequency of application of topical cyclosporine which is associated with an intolerable burning sensation. Poor cooperation, particularly in children or a decrease in drug concentration from 2% to 0.5% could lead to decreased burning sensation but also to a weaker effect.

This study has many different aspects of prospective and observational study. The numbers in the cross-over randomized part are very small. The observers of signs during the eye examination were not blind to the type of treatment given. From this preliminary report, it is therefore not possible to draw any conclusions as to the efficacy of cyclosporine compared to lodoxamide or steroid treatment.

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