

Original Article

Assessment of Drug Usage Pattern in Patients Treated for Vernal Keratoconjunctivitis Attending a Tertiary Eye Care Centre in Eastern India: A Cross-Sectional Study

Aditi Maitra¹, Shashwat Bhattacharyya², Arunava Biswas³, Swapan Kumar Samanta⁴,
Shatavisha Mukherjee¹, Nikhil Era¹

¹Department of Clinical & Experimental Pharmacology, Calcutta School of Tropical Medicine, Kolkata, West Bengal, India.

²Department of Ophthalmology, Calcutta National Medical College, Kolkata, West Bengal, India

³Department of Pharmacology, Calcutta National Medical College, Kolkata, West Bengal, India.

⁴Department of Ophthalmology, Burdwan Medical College, Burdwan, West Bengal, India.

Abstract

Introduction: Vernal keratoconjunctivitis is a recurrent, seasonal, allergic condition affecting children and adolescents in warmer regions worldwide. **Objective:** To assess the drug usage pattern for the management of vernal keratoconjunctivitis (VKC). **Materials & Methods:** This was a 12 weeks long hospital based cross sectional study conducted in the outpatient unit of the department of ophthalmology of a teaching hospital. It included all consecutive patients diagnosed with VKC who satisfied the inclusion criteria. Patients underwent clinical examination and the severity of their disease was graded. Their prescriptions were scanned for duration of therapy, total number of medications, route of administration, the frequency of dosage and change in medications if any, generic names of drugs being prescribed or not and all demographic parameters were recorded in a suitable record form. A p value of <0.05 was considered to be statistically significant. **Results:** 248 patients were enrolled in this study of whom the majority were male (172). The average age of the patients was 8.27 years (SD ± 3.02 years). The mean duration of disease was 15 months (SD ± 9.13 years). The greatest number of children belonged to severity grade 1 (27.82%). The total number of drugs prescribed in this study was 583 with an average of 2.26 drugs per encounter. The commonest prescribed drugs were topical anti-allergics (26.75%) followed closely by lubricants (25.73%) and topical steroids (21.42%). **Conclusion:** Anti allergics and lubricants are the mainstays in the management of VKC. The current study is reflective of this. Clearer guidelines need to be formulated for the better and rational management of VKC.

Key words: Allergic conjunctivitis, Ocular anti allergics, prescribing pattern, rational drug prescription.

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Corresponding author

Shashwat Bhattacharyya

Department of Ophthalmology, Calcutta National Medical College, Kolkata, West Bengal, India.

Mobile: +91-9874624866;

E-mail: bhattacharyya.shashwat@gmail.com

Introduction

Vernal keratoconjunctivitis (VKC) is a bilateral, usually seasonally recurrent, allergic inflammation of the conjunctiva, characterised by limbal gelatinous hypertrophy and/or upper tarsal giant conjunctival papillae usually affecting children and pre pubertal adolescents.

There is a predilection for males to be affected (Leonardi A et al, 2006). The high prevalence of VKC in tropical conditions has been well documented in various studies (McMoli TE et al 1991; Diallo JS et al, 1976; Resnikoff et al 1988). It can present as purely palpebral or purely limbal disease, but a range of mixed appearances exist (Sanford-Smith JH et al, 1979). Most severe cases show corneal signs of inflammation, ranging from superficial punctate keratitis to corneal ulcers, which can lead to visual impairment (Bonini S et al, 2000). The underlying pathogenesis of VKC is primarily due to IgE mediated type 1 hypersensitivity but alternative theories exist which point towards endocrinal, neurological, genetic, socioeconomic as well as environmental causes (Leonardi A et al, 2006). This uncertainty in determining the underlying pathology means that no single drug or a single group of drugs is effective against VKC when used alone.

It is often the treating ophthalmologists' dilemma to choose the most effective treatment and this forces them to prescribe multiple drugs (Sacchetti M, 2010). The more severe cases are routinely treated with corticosteroids. The maintenance therapy is primarily done with anti allergic drugs like H1 antihistaminics or mast cell stabilisers. Recently immunomodulation by topical ciclosporin drops or tacrolimus ointment has been studied to good effect while treating VKC (De Smedt S et al, 2012; Tam PMK et al, 2010). There are also adjunctive roles of oral NSAIDs like aspirin (reduces inflammation) and anti-helminthic therapy (Ajaiyeoba A et al, 2005). Many studies have been undertaken to find out the roles of oral anti-histaminics like monteleukast (Lamiase A et al, 2003), periocular steroid injections (Singh S et al, 2001) and oral ciclosporin (Gokhale NS et al, 2012) in refractory cases of VKC. Although there are treatment guidelines based on large population based studies (Bonini S et al, 2000) the clinical outcomes are

not always predictable. The patients are often stigmatised by the duration, cost and multiple agents used in therapy. The management of VKC remains a formidable challenge owing to the uncertain pathophysiology of the disease. The available literature and data show a role for both pharmacological as well as non pharmacological interventions (Bilkhu PS et al, 2012). Even placebo seems to work, but the problem remains as to whom to treat with anti allergics and whom with steroids. Despite the generous availability of previous literature on the efficacy of drugs used in VKC, the majorities of them were not randomized or had inadequate control groups or were limited to a single centre only (Mantelli F et al, 2007). There is a dearth of clinical data when it comes to large population based studies on the prescribing trends of drugs in VKC. Drug utilisation studies in VKC have many potential benefits. Such studies provide data on the pattern of drug prescription and their rational prescribing trends, profile of adverse drug reactions with these drugs and the cost of therapy keeping in mind the long duration and chronic nature of the disease (Jain S et al, 2015). This information may be used to formulate clinical prescribing guidelines. The available literature on the utilisation aspect of these drugs is grossly inadequate and as such no study has been carried out in India to the best of the author's knowledge.

The present study was thus designed to assess the drug usage pattern using WHO core drug use indicators in patients being treated for vernal keratoconjunctivitis attending a tertiary eye care unit in Eastern India (*World Health Organization, 2002. Promoting rational use of medicines: core components*).

Materials and methods

This was a 12 weeks long (February to April 2016) hospital based cross sectional study conducted in the outpatient unit of the department of ophthalmology of a teaching

hospital in West Bengal, India. After prior approval from the institutional ethics committee all previously diagnosed or newly diagnosed patient of VKC (whether active or quiescent), of either sex and irrespective of age, parents/legal guardians willing to give informed consent were included in the study based on following characteristics (Sangwan VS et al, 2011). VKC Active Type: Active VKC was diagnosed based on the complaint of ocular itching in the presence of upper tarsal conjunctival papillae and/or limbal hypertrophy with bulbar conjunctival pigmentation. VKC Quiescent Type: The quiescent form was diagnosed on the basis of inactive upper tarsal conjunctival papillae and/or scarring and a previous history of ocular itching. The patients were then clinically graded on a scale of 0 to 5 based on the classification suggested by Bonini et al, 2007.

All patients with pre-existing hyperemia & dry eye disease, history of any ocular surgery or laser procedure, history of any chemical/thermal/mechanical trauma preceding the disease, uncooperative patients, contact lens users, ocular inflammation or infection in the preceding 3 months, having history of conjunctivitis other than VKC and one eyed patients were excluded from the study.

A sample size of 225 patients was deemed feasible considering the duration of this study (with an alpha error 7 beta error of 0.05 and 0.20 respectively; power = 80%), based on previous outpatient attendance records. Prescriptions were scanned for patients receiving therapy for VKC duration of therapy, total number of medications, route of administration, the frequency of dosage and change in medications if any, generic names of drugs being prescribed or not. The demographic parameters of the patients were noted. Clinical examination included history taking, visual acuity assessment and examination under slit lamp, applanation tonometry, gonioscopy and 90D Biomicroscopy were done. The eye with

better best corrected visual acuity (BCVA) was included for this study. The demographic data collection was performed with the help of a suitable case report form which included all relevant information.

Data were collected, checked for completeness, compiled and statistically analyzed using Microsoft Excel, Statistical software Package for Social Sciences SPSS (ver. 22). A P value < 0.05 was considered as significant with a 95 % Confidence interval.

Results

A total number of two hundred and forty eight (248) patients were studied of which seventy six (30.65%) patients were female whereas one hundred and seventy two (69.35%) were male patients (M: F=2.26:1). The parents of 2 participants declined to give consent. The average age of the patients was 8.27 years (range 3-16 years, \pm SD 3.02 years). 153 patients hailed from rural areas whereas 95 came from urban or semi urban areas. About 110 (42.63%) patients had a personal history of atopy and 66 (26.61%) had a family history of atopy. The mean duration of disease was 15 months (SD 9.13 months) with a range of 2 months to 48 months. Average best corrected visual acuity was 0.15 (logMAR). The clinical severity gradation of all patients is represented in Figure 1.

The total number of drugs prescribed in this study was 583 with an average of 2.26 drugs per encounter. 26 different formulations were prescribed which included both systemic and topical medications either as monotherapy or in fixed dose combinations (Figure 2; Table 1, 2, 3). The number of prescriptions of topical anti allergic medicines in grade 0, 1, 2A, 2B, 3, 4 and 5 was 12, 41, 27, 35, 23, 05 & 12 respectively (Table 3). For lubricants the numbers were 14, 32, 19, 41, 23, 15 & 06 and for topical corticosteroids the numbers were 06, 35, 31, 23, 15, 13 & 02 respectively.

Immunomodulators were not prescribed in grades 0 and 1. Their prescriptions were noted to be 03, 25, 17 and 12 in groups 2A, 2B, 3 and 4 respectively.

The majority of the drugs were prescribed by their generic name (n= 519, 89.14%). More than half of the patients or their guardians (n= 148, 59.69%) had the correct knowledge of the drug dosages. The drugs used from NLEM (National List of Essential Medicines) India 2015 were oral prednisolone, topical prednisolone, topical carmellose and oral cetirizine.

Discussion

In this study we have tried to bridge the gap between the randomized controlled trials and the real world scenario by objectively studying

the drug prescriptions and quantifying them as per the clinical grade of disease. The present study was conducted in patients diagnosed with VKC, attending the outdoor setup of ophthalmology department in a tertiary eye care unit, where they were assessed at their point of interception for drug usage pattern following various indicators. With a total population of 248 study participants where 69.35% were males, the study shows resemblance with global prevalence. Overall, the average number of drugs per encounter was 2.26, which was slightly on a higher note than the ideal expected range of 1.6-1.8 (Isah AO et al, 2008). A higher average number of drugs prescribed might be due to lack of sensitization of the prescribers regarding rational prescribing.

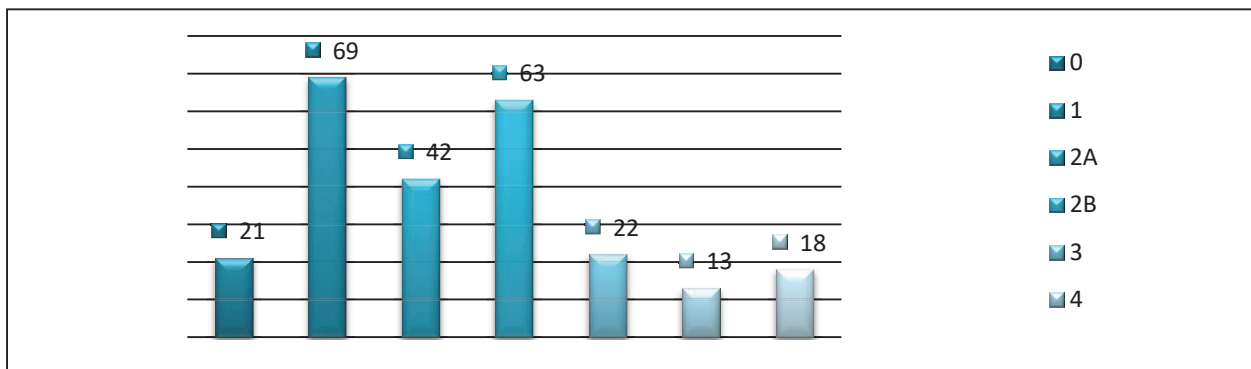


Figure 1: Distribution of patients in each grade of VKC

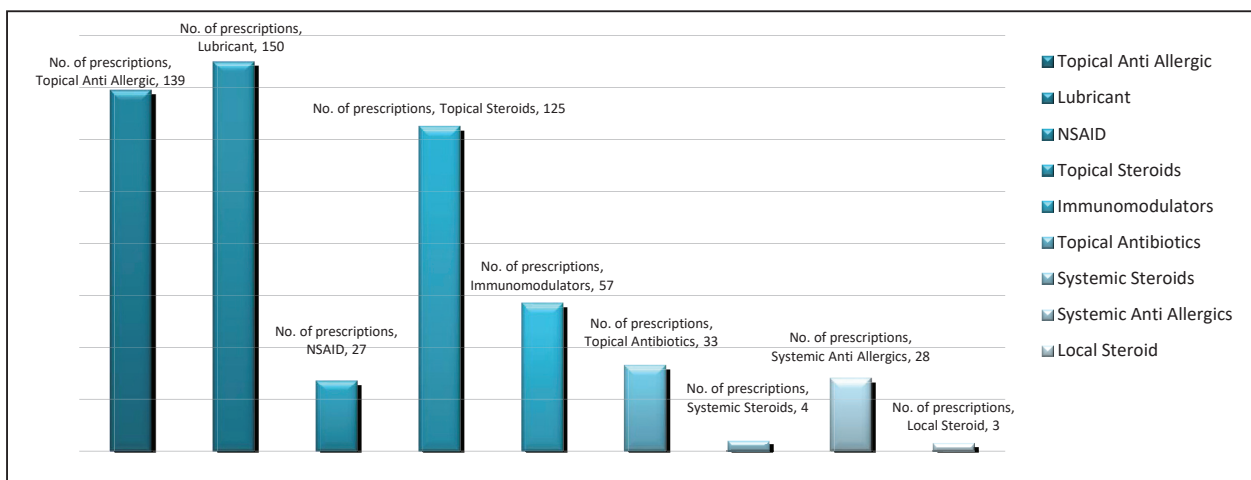


Figure 2: Number of prescriptions in each drug category

Table 1: Drug prescribing pattern in patients treated for vernal keratoconjunctivitis

Frequency of Prescription	Percentage frequency (Total N= 583)		
	MONOTHERAPY	FIXED-COMBINATION	
Topical Medications			94.01
H1 Antihistaminics			3.07
Azelastine 0.05%	4	0	0.68
Bepotastine 1.5%	6	0	1.02
Epinastine 0.05%	8	0	1.37
Combined anti histaminic and mast cell stabilizer			20.75
Ketotifen 0.025%	5	0	0.86
Olopatadine 0.1%	81	17	16.81
Olopatadine 0.2%	18	0	3.08
Mast Cell stabilizer			2.92
Sodium cromoglycolate 4%	17	0	2.91
Lubricants			25.73
Carmellose 0.5%	91	0	15.61
Carmellose 1%	21	0	3.60
Hypromellose 0.3%	34	0	5.83
Poly ethylene glycol 0.4%+ propylene glycol 0.3%	0	4	0.68
NSAID			4.63
Ketorolac 0.4%	15	12	4.63
Topical steroids			21.44
Loteprednol 0.2%	69	8	13.20
Loteprednol 0.5%	6	0	1.03
Fluorometholone 0.1%	10	4	2.40
Dexamethasone 1%	0	21	3.60
Prednisolone 1%	7	0	1.20
Immunomodulators			9.78
Cyclosporine 0.05%	20	0	3.43
Tacrolimus 0.03%	37	0	6.35
Topical Antibiotics			5.66
Moxifloxacin 0.5%	12	5	2.92
Gatifloxacin 0.3%	4	0	0.68
Tobramycin 0.3%	0	12	2.06
Systemic Medication			5.49
Oral Prednisolone tab (1mg/Kg B. Wt.)	4	0	0.68
Ceterizine 5 mg/ 10mg tab	16	0	2.74
Levoceterizine 5 mg tab	12	0	2.06
Local Medication			0.51
Inj Triamcinolone 10mg	3	0	0.51

Table 2: Assessment of Drug usage pattern as per WHO core drug use indicators (*Current Index of Medical Specialties, July-October 2016. UBM Medica India Pvt. Ltd. 2016.)

Class	Indicators	Observed Value
Prescribing Indicators	Average number of drugs per encounter	2.26
	Percentage of drugs prescribed by generic name	89.14%
	Percentage of encounters with an antibiotic prescribed	13.30%
	Percentage of encounters with an injection prescribed	3.10%
	Percentage of drugs prescribed from essential drug list (NLEM 2015)	37.98%
Patient Care Indicators	Average consulting time	Not determined
	Average dispensing time	Not determined
	Percentage of drugs actually dispensed	Not determined
	Patients knowledge of correct dosage	59.69%
Facility Indicators	Availability of copy of EDM NLEM 2015	Yes
	Availability of Key Drugs	Yes
Complementary Indicators	Percentage of patients treated without drugs	0
	Average drug cost per encounter (Vide CIMS 2016)	Rs. 76/- *

Table 3: Drug prescribing pattern according to VKC grading (Bonini S et al, 2007)

DRUG DETAILS	VKC Grade						
	0 (n-21)	1 (n-69)	2A (n-42)	2B (n-63)	3 (n-22)	4 (n-13)	5 (n-18)
Anti allergics	12	41	27	35	23	05	12
Lubricants	14	32	19	41	23	15	06
Topical steroids	06	35	31	23	15	13	02
Topical NSAIDs	04	02	06	14	01	00	00
Topical Immunomodulators	00	00	03	25	17	12	00
Topical antibiotics	02	14	11	06	00	00	00
Oral anti allergic	00	08	09	06	04	01	00
Systemic steroids	00	00	00	00	00	04	00
Local steroids	00	00	00	00	00	03	00

Historically in VKC, the mast cell stabilisers sodium cromoglycate and lodoxamide, have been shown to be very effective based on current clinical outcomes and safety profile (Mantelli F et al, 2007). However in our study we found that combined action anti allergics like olopatadine were more frequently prescribed in comparison to mast cell stabilisers alone, the reason for which remains to be explored. Ocular lubricants

were the second most widely prescribed drugs (25.73%) probably due to their adjunctive role in prevention of dry eyes (Hom MM et al, 2012) and corneal toxic response in VKC. They also prevent development of medicamentosa on prolonged topical drug usage. The lower grades were primarily treated with anti allergic and lubricant drops which was consistent with most recommendations (Bonini S et al, 2007). In

more severe cases topical steroid therapy with high potency molecules like dexamethasone or prednisolone were required as has been reported previously (Kumar S, 2009). We have also observed a trend of prescribing low potency steroids like loteprednol, in very early grades of VKC. The use of ketorolac tromethamine, was found to have been lesser in comparison to earlier reports (Mantelli F et al, 2007). The interesting thing to note about immunomodulators prescriptions in this study was the trend to apply them in intermediate grades of VKC (Grades 2b & 3) in greater numbers than topical steroids. This shows a clear shift in prevalent management trends which mirrors their efficacy as reported in trials (Dumrongkigchaiporn P et al, 2004; Daniell M et al, 2006). The use of systemic steroids and local steroid injections was reported from a handful of very severe cases and establishes their role in the management of such cases only. One potential controversy was encountered when the use of systemic anti allergic medications were reported in fair number of cases. They have been reported to cause dry eyes and their role in the management of ocular allergies is debatable (Bielroy L et al, 2005). The irrationality of prescribing antibiotics in the management of VKC is exemplified in this study (33 prescriptions), where coexistent ocular infection was an exclusion criterion. They have no role in the management of ocular allergy alone where there is no secondary infection. One important finding was the complete absence of anti helminthic medicines from all the prescriptions, which are reported to have adjunctive role in the management of VKC (Ajaiyeoba A, 2005).

In the absence of clear guidelines and protocols, the recommendations of Bonini et al 2007 and Leonardi, 2013; are useful in formulation of treatment protocols by the treating ophthalmologists.

Limitations

This study is hamstrung by the small size of study population and is not multicentric. It cannot claim to be representative of national let alone regional trends. The duration of this study could have been more to better reflect annual trends of both disease pattern and prescription trends. Such studies should be taken up on a larger scale on a multicentric basis to be truly representative of the actual trends. Our study also did not have a mandate to study therapeutic risk benefit of individual drugs in the real world scenario. Another major flaw was the setting being in the OPD thus ruling out the better appreciation of WHO facility indicators. We also acknowledge the lack of information on the non pharmacological measures of controlling VKC in these patients and any role they might have on the clinical grading.

Conclusion

It will be prudent to state that this study has clearly demonstrated the gap between clinical trials and real world prescribing trends of drugs in the management of VKC. The maximum numbers of prescriptions were of topical anti allergic drops with of lubricating drops being the second most prescribed group. There have to be clearer guidelines and consensus for the diagnosis and management of VKC as per the clinical grade of the disease.

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