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A Double-Masked Comparison Of 0.1% Tacrolimus Ointment And 2% Cyclosporine Eye Drops As First Line Drugs in the Treatment of Vernal Keratoconjunctivitis

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Abstract: *This study was carried out to compare the efficacy of 0.1% Tacrolimus (FK-506) ophthalmic eye ointment with 2% Cyclosporine eye drops in the treatment of VKC. Two groups of VKC diagnosed patients was taken for study-Group A:36 patients received 0.1% tacrolimus eye ointment and Group B:36 patients received 2% cyclosporine eye drops. The study was conducted in Ophthalmology Department, Rajindra Hospital, Patiala. Patients fulfilling the inclusion criteria and after verifying the exclusion criteria were enrolled in the study. The main outcome measures were scoring and comparison of Total subjective symptom scores (TSSS) and Total objective ocular sign scores (TOSS) within and between the Groups at each follow up. With treatment both TSSS and TOSS decreased consistently in both groups without any adverse effects but an increase in scores was noticed within two weeks after drug withdrawl. Both drugs are equally effective and safe in VKC but with a short lasting effect.*

I. Introduction

Vernal keratoconjunctivitis (VKC) is a chronic sight-threatening inflammatory eye disease commonly observed in children and adolescents. VKC usually occurs before 10 years of age. The disease generally lasts 2-10 years and ordinarily resolves by puberty.[1]

Epidemiology

VKC is more frequent in warmer, arid, windy climates, in the Mediterranean area, central Africa, Japan, India, and South America but is also reported in North America, China, Australia, Great Britain, and Sweden. VKC appears mainly seasonally but can be perennial, chronic or with acute exacerbations.[2] VKC commonly occurs in school-age children. Often, patients have suffered the affliction for 3–4 years before being properly diagnosed.[3] A male preponderance has been observed, especially in patients under 20 years of age, among whom the male:female ratio is 4:1–3:1[2,4], whereas the ratio in those older than 20 years of age is 1:1. [2, 4, 5]

Histopathogenesis

VKC is characterized by conjunctival infiltrations with eosinophils, degranulated mast cells, basophils, plasma cells, lymphocytes, and macrophages. T cell culture from conjunctival scraping of VKC patients yielded mainly Th2-type clones.[6] Th2-derived cytokines such as IL-4, IL-5, IL-13, growth factors and enzymes are found in the conjunctiva of VKC patients.[7] Increased production of Th2 cytokines in VKC may contribute, in part, to tissue remodelling and papillary formation on tarsal conjunctiva.[8]

Types

The disease may present in three clinical forms: tarsal, limbal and the mixed form. Large papillae of different shape and size, usually greater than 1 mm in diameter, on the upper tarsal conjunctiva characterize the tarsal form, while Tranta's dots and infiltrates on the limbus are typical of the limbal form. The mixed form is characterized by the presence of both forms in the same eye.

Symptoms

Severe itching and photophobia are the main symptoms. Associated foreign body sensation, ptosis, thick mucus discharge, and blepharospasm occur.

Signs

The signs are confined mostly to the conjunctiva and cornea; the skin of the lids and lid margin are relatively uninvolved compared to AKC. The conjunctiva develops a papillary response, principally of the limbus or upper tarsus. The tarsal papillae are discrete, greater than 1 mm in diameter, have flattened tops that may stain with fluorescein, and occur more frequently in European and North American patients.[11] Thick, ropy mucus tends to be associated with the tarsal papilla . These are the classic 'cobblestone' papillae. Limbal papillae tend to be gelatinous and confluent, and they occur more commonly in African and West Indian patients.[12] Horner-Trantas dots, which are collections of epithelial cells and eosinophils, may be found at any meridian around the limbus.[14] These changes may lead to superficial corneal neovascularization. The forniceal conjunctiva usually does not show foreshortening or symblepharon formation. The corneal findings may be sight threatening. Buckley describes in detail the sequence of occurrence of corneal findings.[11] Mediators from the inflamed tarsal conjunctiva cause a punctate epithelial keratitis. Coalescence of these areas leads to frank epithelial erosion, leaving Bowman's membrane intact. If, at this point, inadequate or no treatment is rendered, a plaque containing fibrin and mucus deposits over the epithelial defect.[13] Epithelial healing is then impaired, and new vessel growth is encouraged. This so-called shield ulcer usually has its lower border in the upper half of the visual axis. With resolution, the ulcerated area leaves a subepithelial ringlike scar. The peripheral cornea may show a waxing and waning, superficial stromal, gray-white deposition termed pseudogerontoxon. Iritis is not reported to occur in VKC.

Diagnosis

VKC is not difficult to diagnose by clinical examination. Tranta's dots and large cobblestone papillae are indicative of the condition.[9,10] VKC is differentiated from other ocular allergic conditions, such as SAC,PAC, AKC, ocular rosacea in children and infectious conjunctivitis, through a comprehensive clinical history and ophthalmic examination. It is important to note that while skin test results may be positive, VKC is not always closely related to allergen exposure, and climate is an equally important factor. Conjunctival scrapings or tear cytology can be useful, revealing increased leukocytes in the conjunctiva, particularly eosinophils.[9,10]

Treatment

The treatment of vernal keratoconjunctivitis can be done with:

1. Cromolyn and the new generation of antiallergic compounds such as alomide tromethamine, nedocromil sodium, spaglumic acid, and topical antihistamines are effective in reducing signs and symptoms of the disease.[15]
2. Nonsteroidal anti-inflammatory agents also produce a beneficial effect on the course of VKC.[16]
3. Topical steroid preparations are naturally the most effective therapy for moderate to severe form of VKC.[17,18]
4. Cyclosporine A (CsA) from 0.5 to 2% ophthalmic emulsions in olive or castor oil, used four times daily, represents a valid alternative to steroids in severe forms of VKC. In fact, CsA is effective in controlling ocular inflammation, blocking Th2 lymphocyte proliferation, and IL-2 production. It also inhibits histamine release from mast cells and basophils and, through a reduction of IL-5 production, it may reduce the recruitment and the effects of eosinophils on the conjunctiva.[19,20,21,22]
5. Tacrolimus is a macrolide immunomodulatory agent (previously known as FK506), which is similar to cyclosporine A in its functional mechanism, butwith about 100-fold higher potency. Tacrolimus binds to steroid receptors on the cell surface, inhibiting the release of mediators from mast cells, suppressing T-cell activation, and T-helper-cell mediated B-cell proliferation. In addition, it also causes a decrease in intracellular adhesion molecules and reduced formation of cytokines, especially interleukin-2. [23-31]

II. Material And Methods

All patients had active VKC on enrollment. Diagnosis of VKC was made clinically according to the commonly accepted criteria. After getting clearance from the ethical committee, written informed consent was taken from the patients. Complete general, physical and ophthalmologic examinations were done. They were advised to discontinue all topical and oral allergic drugs for 2 weeks. After two weeks the patients were examined and their baseline symptoms (TSSS) as well as signs (TOSS) were recorded and were randomly assigned to one of the two study groups. -

Group A - Tacrolimus ointment (0.1%) BD, preservative free artificial tears and cold compression for 6 weeks.
Group B- Cyclosporine (2%) QID, preservative free artificial tears cold compression for 6 weeks.
FOLLOW UP – Fort nightly for 10 weeks (6 weeks with treatment and 4 weeks after withdrawal of drugs).
The main outcome measure was measured in terms of Total subjective symptom scores (TSSS) and total

objective ocular sign score (TOSS) before and after treatment at each visit. Secondary outcomes included side effects (transient and long term) of medications and recurrence of symptoms and sign.

Clinical Scoring System Grading of Symptoms (Bleik et. al.)[32]
Symptoms of itching, tearing, photophobia, discharge and foreign body sensation was recorded before and after treatment

Symptoms were graded as follows:

0= indicating no symptoms
1+= mild symptoms of discomfort which were just noticeable.
2 + = moderate discomfort noticed most of the day but did not interfere with daily routine activities.
3+ = severe symptoms interfering with daily routine activities

Grading of Signs conjunctival hyperemia

0 = no evidence of bulbar hyperemia.
1+ = mild bulbar hyperemia.
2+ = moderate bulbar hyperemia.
3+ = severe bulbar hyperemia.

Palpebral conjunctival papillae

0= no papillary hypertrophy of the palpebral conjunctiva.
1+ = mild papillary hypertrophy.
2+ = moderate papillary hypertrophy (hazy view of the deep tarsal vessels).
3+ = severe papillary hypertrophy (deep tarsal vessels not visible in more than 50% of the surface).

Punctate keratitis

0= no evidence of punctate keratitis.
1+ = one quadrant of punctate keratitis.
2+ = two quadrants of punctate keratitis.
3+ = three or more quadrants of punctate keratitis.

Trantas'dots were graded as follows:

0 = no evidence of dots.
1+ = 1 to 2 dots.
2 + = 3 to 4 dots.
3 + = more than 4 dots.

Limbal infiltration

0 = no evidence of limbal infiltrates.
1 + = less than 90̊ of limbal infiltrates.
2 + = less than 180̊ of limbal infiltrate but more than 90̊.
3 + = more than 180̊ of limbal infiltrate.

Conjunctival inflammation and allergic ocular symptoms example itching, swollen eyes, burning, stinging, discharge, tearing, foreign body sensation & photophobia were evaluated prior to initiation of treatment and then reviewed weekly at subsequent visits. Allergic ocular signs like lid oedema, conjunctival chemosis, conjunctival injection, conjunctival mucus strands and keratits were evaluated before initiation of treatment and then reviewed weekly. All allergic symptoms and signs were rated using a scale from 0 to 3 i.e. allegry symptoms were rated as 0 for none, 1 for mild, 2 for moderate, 3 for marked while signs were rated as 0 for none, 1 for mild, 2 for moderate, 3 for severe.

Statistical Analysis

All data were analyzed by a statistical software package (SPSS11.0). Comparison of TSSS, TOSS and side effect scores between and within group at different time points (at entry, weeks 2, 4, 6, and 10) was performed by ANOVA with repeated measure analysis and with Bonferroni corrections. A p value of less than 0.05 was considered statistically significant. Associated allergic diseases between two groups were compared by Fisher's exact test.

III. Results

Seventy two consecutive VKC patients presenting to our institute(June 2015 - April 2017) were enrolled into this study but only 56 patients completed this study with mean age 8.18 ± 1.64years (Range 5-12 years, Table 1). The difference in the mean age of both the groups was statistically insignificant (p=0.45). Most of the patient were male (n= 44) with only 12 females.

Tarsal VKC was the most common form of presentation (n=39) followed by limbal variant (n=13) and mixed type VKC (n=4) and. The Mean duration of symptoms was 16.16±2.84months. There was no statistical difference (p> 0.05) in duration of symptoms between the two group.

TABLE 1

		Tacrolimus (n = 30)	Cyclosporine (n = 26)	P value	Total
Age	**Mean ± SD** **Range**	**8.33 ± 1.69** **6 – 12**	**8.00 ± 1.60** **5 – 12**	**0.454**	**8.18 ± 1.64**
Duration	**Mean ± SD** **Range**	**16.47 ± 3.08** **9 – 22**	**15.81 ± 2.55** **12 - 22**	**0.391**	**16.16±2.84**
Type of VKC	**Tarsal**	**23 (76.7%)**	**16 (61.5%)**	**0.434**	**39 (69.6%)**
	Limbal	**5 (16.7%)**	**8 (30.8%)**		**13 (23.2%)**
	Mixed	**2 (6.7%)**	**2 (7.7%)**		**4 (7.1%)**
Complaints	**Itching**	**30 (100%)**	**26 (100%)**	**-**	**56 (100%)**
	Discharge	**25 (83.3%)**	**20 (76.96%)**	**0.547**	**45 (80.4%)**
	Tearing	**24 (80%)**	**20 (76.9%)**	**0.780**	**44 (78.6%)**
	Photophobia	**12 (40%)**	**14 (53.8%)**	**0.300**	**26 (46.4%)**
	Foreign body sensation	**8 (26.7%)**	**9 (34.6%)**	**0.519**	**17 (30.4%)**
Associated allergic diseases	**Eczema**	**1 (3.3%)**	**2 (7.7%)**	**0.470**	**3 (5.4%)**
	Asthma	**3 (10%)**	**1 (3.8%)**	**0.373**	**4 (7.1%)**
	Allergic rhinitis	**6 (20%)**	**5 (19.2%)**	**0.942**	**11 (19.6%)**
Family History	**Present**	**1 (3.3%)**	**1 (3.3%)**	**0.918**	**2 (3.6%)**
TSSS (baseline)	**Mean ± SD** **Range**	**7.43 ± 0.97** **5 – 9**	**6.96 ± 0.96** **5 – 9**	**0.074**	**7.21 ± 0.99** **5 – 9**
TOSS (baseline)	**Mean ± SD** **Range**	**4.13 ± 1.17** **2 – 6**	**4.19 ± 0.63** **3 – 5**	**0.819**	**4.16 ± 0.95** **2 – 6**

The five major complaints recorded by patients were itching (56 patients, 100%), discharge (45 patients), tearing (44 patients), photophobia (26 patients) and foreign body sensation (17 patients). Associated allergic diseases noted were allergic rhinitis (20%), asthma (7.2%) and atopic dermatitis (5.4%). There was reduction in TSSS in both the groups from 2 weeks onwards and the difference became statistically significant at 4 weeks (p<0.05) and was maintained till the completion of the course (6 weeks). But the difference was not significant between the two groups (p=0.52). Comparisons of TSSS between the two groups were shown in Table 2. Reduction of TOSS was decreasing in subsequent visit and it was statistically significant at week 6th week in the FK-506 group (p<0.01). No difference in TOSS between the two treatment groups was observed at any time points.

Total Subjective Symptom Scores (TSSS) at different visits

Time	Group A			Group B			Group A vs B (p value)
	Mean ± SD	Change from baseline	P value	Mean ± SD	Change from baseline	P value	
Baseline	**7.43 ± 0.97**	**-**	**-**	**6.96 ± 0.96**	**-**	**-**	**0.074**
2nd week	**4.30 ± 1.02**	**3.13 ± 0.73**	**<0.001****	**3.77 ± 0.86**	**3.19 ± 0.75**	**<0.001****	**0.042***
4th week	**2.50 ± 0.73**	**4.93 ± 0.74**	**<0.001****	**2.12 ± 0.71**	**4.85 ± 0.83**	**<0.001****	**0.052**
6th week	**1.27 ± 0.45**	**6.17 ± 0.91**	**<0.001****	**1.19 ± 0.40**	**5.77 ± 0.91**	**<0.001****	**0.520**
10th week	**2.43 ± 0.86**	**5.00 ± 1.08**	**<0.001****	**2.42 ± 0.81**	**4.54 ± 1.27**	**<0.001****	**0.964**

Total Objective Symptom Scores (TOSS) at different visits

Time	Group A			Group B			Group A vs B (p value)
	Mean ± SD	Change from baseline	P value	Mean ± SD	Change from baseline	P value	
Baseline	**4.13 ± 1.17**	**-**	**-**	**4.19 ± 0.63**	**-**	**-**	**0.819**
2nd week	**3.40 ± 0.81**	**0.73 ± 0.64**	**<0.001****	**3.35 ± 0.63**	**0.85 ± 0.54**	**<0.001****	**0.785**
4th week	**3.20 ± 0.66**	**0.93 ± 0.91**	**<0.001****	**3.08 ± 0.48**	**1.12 ± 0.71**	**<0.001****	**0.438**
6th week	**2.07 ± 0.74**	**2.07 ± 0.87**	**<0.001****	**2.04 ± 0.60**	**2.15 ± 0.68**	**<0.001****	**0.877**
10th week	**3.17 ± 0.59**	**0.97 ± 0.93**	**<0.001****	**2.92 ± 0.63**	**1.27 ± 0.83**	**<0.001****	**0.141**

Conjunctival hyperemia was significantly decreased in both the groups at 4th and 6th week. But no significant difference in papillae (size or number) was detected even at 6th week of treatment in either group. At 10th week (after 4 weeks of discontinuing treatment) increase in TOSS was observed in both the groups which was statistically significant. Recurrence was observed more in tacrolimus group.

Side effects
No ocular or systemic side effects were noted in either group.

IV. Discussion

In our study both 0.1% Tacrolimus and 2% Cyclosporine cause a reduction in TSSS from 4th week onwards. A similar prospective, double-masked, randomized comparative study was conducted by Rashmi kumara et al(33) in 2016 in which 19 patients received 0.03%Tacrolimus eye ointment daily for 6 weeks and other 15 recieved 0.05% Cyclosporine eye drops four times daily for 6 weeks. This study reported that tacrolimus brought about an improvement of the signs and symptoms of VKC similar to that of cyclosporine A. .Objective ocular signs were found to be more improved with tacrolimus treatment, even though this was not statistically significant. Our study didn't show any significant difference between the efficacy of the two drugs .At the same time there was no ocular side effects in either group. Another study conducted by Panadda Labcharoenwongs et al(34) in 2012 with patients receiving 0.1% Tacrolimus eye ointment twice daily and 2% Cyclosporine eye drops four times daily showed a significant decrease in TSSS, compared to their baselines, at weeks 4 and 8, in both treatment groups. However, no statistical difference in TSSS was noted between groups at any time point. Total ocular sign scores (TOSS) in the FK- 506 group decreased significantly at weeks 4 and 8 compared to baseline. Although there was a decrease of TOSS in the cyclosporine group, the difference did not reach statistical significance. Topical cyclosporine of various concentrations has been investigated for VKC treatment with varying results. In a 2-week, doublemasked,placebo-controlled trial by Pucci et al,topical cyclosporine 2% resulted in an approximately 40% reduction in subjective and objective scores by the end of the randomization period.[35] Same concentration of cyclosporine eye drop was tried in a large number of children with VKC from Rwanda, Africa.[36] In that study, cyclosporine 2% eye drop was shown to be as effective as topical dexamethasone during the 4-week study period. In a longer open trial by Spadavecchi et al utilizing a lower concentration of cyclosporine (1.25% and 1%) for 4 months, a higher degree of benefit in subjective and objective was observed.[37] Recently, a randomized, placebo-controlled trial of tacrolimus 0.1% solution in severe allergic conjunctivitis (41 AKC and 14 VKC) was reported.[38] All patients responded to this novel preparation of tacrolimus. As with tacrolimus ointment, the effect from solution could clearly be seen as early as 1 week of treatment. Most interesting finding from this later report was the resolution of giant papilla with tacrolimus treatment. Such finding was seen in some of our patients in our current study as well as in our previous study, indicating that tacrolimus could potentially alter the natural course of both AKC and VKC. Difference in efficacy of cyclosporine in various publications could be due to difference in methods for cyclosporine preparation and to difference in disease severity. No literature at present mentions about the course of the disease after stopping treatment with respect to concentration and duration which needs to be further investigated to exactly quantify the duration of treatment for most effective outcome taking care off the side effects of these immune modulators on long term use. The limitations of our study is a small sample size, short course of treatment.Also since 12 out of 72 patients were lost to follow up,not much can be commented on the side effects of the drugs .

V. Conclusion

According to our study, Tacrolimus ophthalmic ointment(0.1%) twice daily brought about an improvement of symptoms of VKC similar to that of 2% cyclosporine eye drop four times daily. Both have potentials to be used as first line drugs that too with equal efficacy as there was significant decrease in TSSS and TOSS at 6th weeks. However, the effect of the drug is very short lasting. Hence, further research work needs to be done on the concentration of the drugs to avoid relapse of the disease.

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