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Original Research Article

A study on the use of tacrolimus eye oitment (0.03%) in allergic eye disease

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ABSTRACT

Aim: To study the effect of 0.03% tacrolimus eye ointment in allergic eye disease
Materials and Methods: This prospective study was conducted on patients suffering from recurrent allergic eye disease. All those patients who used steroids frequently because of recurrence or chronic refractory cases were included in this study. We included 48 cases in this study. Tacrolimus 0.03% eye ointment was used twice daily for 3 months and effect was seen in terms of improvement in symptoms, signs and any recurrence if occurred after stopping treatment.
Results: Mean age of the patient was 21.04 ±7.02 and mean duration of allergic eye disease was 3.52± 0.94. Symptoms and sign scores shown improvement after using tacrolimus eye ointment for 3 months. Itching and redness (88% & 82% respectively) improved dramatically at the end of 1 month. Recurrence was noticed at 6^{th} month follow up in 6 cases after stopping tacrolimus eye ointment so it was restarted. While in 42 cases (87.5%) we didn't notice any recurrence after stopping tacrolimus eye ointment.
Conclusion: Tacrolimus eye ointment (0.03%) is effective in controlling allergic eye disease and is very effective steroid sparing drug in chronic recurrent cases where frequent use of steroids is required.

1. Introduction

Presentation of allergic eye disease may vary from seasonal or perennial allergic conjunctivitis to more chronic forms like atopic conjuctivitis or vernal catarrh with involvement of cornea depending upon severity.[1] Giant papillary conjunctivitis is not a true allergic disorder.

Seasonal allergic conjunctivitis is usually due to pollens and associated with allergic rhinitis or hay fever while perennial form persists all throughout the year and is usually due to insects or dust. Clinical symptoms and signs are usually bilateral and includes itching, lacrimation, redness, photophobia, lid swelling and foreign body sensation and often associated with running nose.

VKC is a chronic phase of allergic conjunctivitis. Patient presents with common findings pertaining to allergic eye disease like severe itching, watering, burning, photophobia and hyperaemia. Apart from that ropy mucus discharge, conjunctival chemosis, papillary hypertrophy (papillae more than 1mm) also known as cobblestone appearance, gelatinous limbal thickening and Trantas's dots on bulbar conjunctiva are some hallmark features. In severe cases fibrosis may develop and can cause symblepharon formation. Corneal signs includes punctuate epithelial keratopathy, macroerosion, ring shaped epithelial scarring and shield's ulcer.

Presentation of VKC in India or tropical countries is relatively different than temperate zones having lesser association with atopy and systemic allergies and significant number of cases present in perennial form.[2,3]

Atopic kerato conjunctivitis is associated with systemic allergic reaction and usually upper respiratory tract involvement or allergic rhinitis. Lid odema, excoriation on skin, itching, redness and papillae are commonly seen. Atopic cataracts are also known and not always related to use of steroids.

Pathophysiology in allergic conjunctivitis is not fully understood. In acute phase there is IgE mediated mast cell

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degranuation and followed by release of histamine, tryptase, prostaglandins and leukotrienes leading to itching, watering and chemosis.

VKC is a chronic allergic inflammation of the ocular surface mediated mainly by Th2-lymphocyte and along with histamine; eosinophils, neutrophils, Th2-derived cytokines, chemokines, adhesion molecules, growth factors, fibroblast and lymphocytes are also secreted and found in tears. Giant papillae are due to IL-3 and IL- 4.[4] Tranta's dots consists of necrotic eosinophils and epithelial cells. The massive eosinophil infiltration and activation in the conjunctiva is responsible for the corneal complications.

There are various treatment options for allergic conjunctivitis. It includes lubricants, antihistaminics, mast cell stabilizers, immunomodulators (cyclosporine & tacrolimus), mitomycin C, topical steroids and oral steroids in severe cases.

Apart from mast cell stabilizers, antihistaminic drugs like olopatadine, bepotastine besilate and azelastine have dual action. These drugsstabilize mast cells and prevents degranulation and antagonise the action of histamine. Bepotastine inhbit leuotriene B4 and check eosinophil release and so acts as anti-inflammatory drugs.

Steroids are most effective but due to chronicity of disease, complications like cataract and glaucoma can't be ignored.

Cyclosporine A is steroid sparing drug acting as a immunomodulator. It can be used in concentration of 0.5% to 2% and higher concentration can be prepared by adding cyclosporin injections to artificial tears. It's use for 7 years duration is being reported.[5]

Tacrolimus (FK-506) is a macrolide antibiotic derived from (streptomyces tsukubaensis) is a potent immunomodulator. It acts primarily on T-lymphocytes by inhibiting production of cytokines particularly IL- 2, checks T-helper-cell mediated B-cell proliferation, inhibits IgE-dependent histamine release from mast cells and basophils. In addition, it also causes a decrease in intracellular adhesion molecules.[6] Both tacrolimus and cyclosporine act on their target cells via cyclophyllin receptors.

Tacrolimus ointment is available in strengths of 0.03% to 0.1%. Conjunctival instillation is associated with irritation so can be applied on skin of eye lids. It's often used as an alteranative to steroids. Weaning off steroids is reported in 50 to 90% cases in different studies. Literature reports it's use successfully for 3 years.[7,8]

Orally tacrolimus was used in rheumatoid arthritis, psoriasis and also in inflammatory bowel disease. It was also used in patients of corneal grafting.

2. Materials and Methods

This study was conducted in department of Ophthalmology, RKDFMCH&RC. Patients with allergic conjunctivitis with recurrent episodes between the age group of 8 to 30 years were included. This study was conducted from August 2018 to Nov 2019 including 6month follow after stopping tacrolimus eye ointment. We included 48 patients (23 male & 25 females) in this study coming to routine ophthalmic OPD and ethical clearance was done. Mean age of the patient was 21.04 $\pm$7.02 and mean duration of disease was 3.52$\pm$ 0.94.

Detailed history of onset of disease, duration, earlier recurrences, drugs used, association with systemic allergies and history regarding seasonal or perennial nature was taken. Detailed examination done including IOP measurement, fundus and slit lamp examination. We gave prednisolone acetate 1% eye drop for 1 month in acute phase and then at the end of 1 month we switched over to tacrolimus eye ointment 0.03% twice a day for 3 months. Baseline scores were noted before starting tacrolimus 0.0 3% ointment, then follow up was done every month till 6 months after discontinuing tacrolimus eye ointment. We noted all the symptoms and signs on the day of presentation and then observed if any improvement was there. We looked for any drug intolerance, side effects, whether it was discontinued and if any recurrence was there after withdrawal of tacrolimus. Symptoms and sign scores were taken at baseline, after 1 month, 3months and at 6^{th} month.

2.1. Inclusion criteria

All patients of recurrent allergic conjunctivitis where steroids were required frequently. We included recurrent cases of seasonal and perennial allergic conjunctivitis, VKC and cases of atopic keratoconjunctivitis.

2.2. Exclusion criteria

Refusal for follow up by patients and patient's on systemic steroids and immunosuppresants

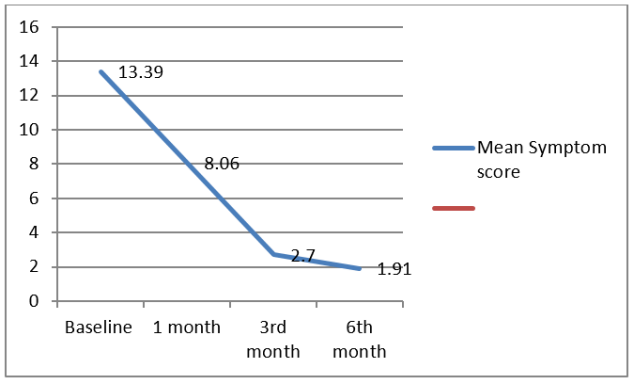

Fig. 1: Mean symptom score showing deviation frombaseline after starting tacrolimus 0.03% eye ointment

Evaluation was done on the basis of symptoms and signs. We have taken 6 symptoms into account including itching, discharge, lacrimation, photophobia, foreign body sensation

Table 1: Demographic profile

Age group	**No of cases**
1-10 years	7
11-20 years	15
21-30 years	26
Sex	
Male	23
Female	25

Table 2: Different signs were also evaluated and tabulated as follows

Signs	**Score**	**Criteria**
Palpebral Hyperaemia	3	Impossible to distinguish individual blood Vessels
	2	Dilatation of many vessels
	1	Dilatation of few vessels
	0	None
Odema	3	Diffuse oedema with opacity
	2	Thinner diffuse oedema
	1	Slight oedema
	0	None
Follicles	3	20 or more follicles
	2	10 – 19 follicles
	1	1 – 9 follicles
	0	None
Papillae	3	Papillae size: 0.6 mm or more
	2	Papillae size: 0.3 – 0.5 mm
	1	Papillae size very small
	0	None
Giant papillae >1mm	3	Elevated papillae in 1/2 or more of the upper palpebral conjunctiva
	2	Elevated papillae in <1/2 of the upper palpebral conjunctiva
	1	Flat papillae
	0	None
Bulbar conjunctiva Hyperaemia	3	Elevated papillae in 1/2 or more of the upper palpebral conjunctiva
	2	Elevated papillae in <1/2 of the upper palpebral conjunctiva
	1	Flat papillae
	0	None
Odema	3	Bullous oedema
	2	Thinner diffuse oedema
	1	Localized oedema
	0	None
Trantas Dots	3	9 > dots
	2	5-8 dots
	1	1-4 dots
	0	None
Thickening	3	Found in 2/3 or more of the limbal circumference
	2	Found in 1/3 to <2/3 of the limbal circumference
	1	Found in <1/3 of the limbal circumference
	0	None
Corneal epithelial signs	3	Shield ulcer or corneal erosion
	2	Macroerosions
	1	Superficial punctate keratitis
	0	None

Table 3: Total subjective symptom score at different visits

	Range of score	No of patients	Min score	Max score	Mean score	Standard deviation
Baseline	0-18	48	12	17	13.39	1.36
1 month	0-18	48	6	15	8.06	1.39
3^{rd} month	0-18	48	0	8	2.70	2.02
6^{th} month	0-18	48	0	8	1.91	1.92

Table 4: Total subjective signs score at different visits

	Range of score	No of patients	Min Score	Max score	Mean score	Standard deviation
Baseline	0-30	48	8	24	15.20	5.16
1 month	0-30	48	5	20	10.87	4.00
3^{rd} month	0-30	48	0	05	1.93	1.13
6^{th} month	0-30	48	0	12	2.00	3.17

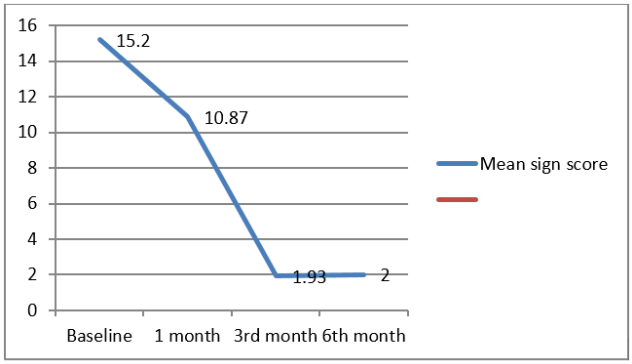

Fig. 2: Mean sign score showing deviation from baseline after starting tacrolimus 0.03% eye ointment

and redness.

Scoring was done the basis of severity (range 0-18)

0= No symptoms 1= Mild 2= Moderate 3= Severe

Scoring was applied for 10 signs also. Similar grading pattern followed from 0 to 3.

Range (0 -30) 0= No signs 1= Mild 2 = Moderate 3= Severe

All this scoring was done at baseline before starting tacrolimus, then at 1^{st} month, 3^{rd} month and 6 months after starting tacrolimus 0.3%. Mean score calculated and deviation from baseline calculated.

3. Statistical analysis

The collected data was entered in excel sheet. All statistical analysis was carried out using SPSS version20 and appropriate statistical tools were used.

4. Results

Out of 51 patients, 48 patients participated and 3 patients discontinued ointment use due to irritation. Out of 48 cases, 20 cases were diagnosed with VKC, 23 cases were diagnosed with perennial and seasonal allergies and there were 5 cases of atopic keratoconjunctivitis. At the end of 1 month after giving tacrolimus (0.03%) eye ointment, itching improved in 88% cases, redness improved in 82% cases, FB sensation in 70% cases, watering in 75% cases, discharge in 70% cases and photophobia in 72% cases. Out of 20 cases of VKC, 8 cases (40%) had papillae and has shown improvement at the end of 3 months. Out of 48 cases, conjunctival hyperaemia (palpebral) improved in 80% cases and hyperaemia of bulbar conjunctiva improved in 75% cases. Recurrence was seen in 6 cases on 6^{th} month follow up so it was restarted for 1 month and improvement was seen. In 42 cases (87.5%) no recurrence was seen even after 6 months after withdrawal of drug. (Tables 3 and 4) Figures 1 and 2

5. Discussion

In day to day practice we come across patients of allergic eye disease. Steroids are most effective and then also because of easy availability, are not used judiciously. Complications like cataract and glaucoma can not be ignored because of prolonged use due to recurrent nature of disease. VKC is mainly seen in younger age group, so recording of IOP is an additional problem.[9,10]

Tacrolimus is steroid sparing and effective in control of different allergic eye disease. It's usefulness in atopic keratoconjunctivitis is reported in different studies.[11,12]

Apart from this it's role in superior limbic conjunctivitis, refractory VKC, post adenoviral subepithelial infiltrates, has been reported in literature.[13–16]

Depending upon the severity of diseases and periodicity of disease, step ladder approach has been proposed by Gokhale et al. They also proposed use of tacrolimus or cyclosporine in moderate or severe cases along with steroids and antihistaminics.[17]

Similar effectiveness has been reported with cyclosporine 2% and 0.1% tacrolimus drops but cyclosporine drops has to be prepared.[18]

We registered 48 patients, most of the patients complained of irritation for few days but later on were able

to tolerate. Only 3 patients discontinued the treatment and were not included further. We used 0.03% ointment on eyelids so tolerance was better.

All the patients included in study were either recurrent cases seasonal or perennial type or refractory cases of VKC. There were 5 cases of atopic conjunctivitis also. All these patients were chronic cases with off and on acute exacerbations and being treated on steroids and antihistaminics frequently though none of them suffered from any complications.

Marked improvement in itching and redness was noticed (88 % and 82%) at the end of one month. Recurrence was seen at 6^{th} month follow up in 6 cases though severity was quite less in comparison to base line values. Tacrolimus 0.3% eye ointment was given for another 1 month and improvement was seen. In 42 cases (87.5%) cases no recurrence was seen even 6months after withdrawal of drug.

6. Conclusion

Tacrolimus 0.03 % eye ointment is a potent steroid sparing drug in recurrent, refractory cases of allergic eye disease so minimising frequent use of steroids.

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9. Conflict of interest

None.

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