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Research Paper

Role of Tacrolimus in treatment of Refractory Vernal Kerato-Conjunctivitis

Mohammed Ather*, Ashok J, Tulasi Priya K, Farha Jabeen, G Udayasree
Professor of Ophthalmology, Bhaskar Medical College, Yenkapalli, Moinabad, RR district, Telangana
Consultant Ophthalmologist, Solis eye care hospital, ECIL, Hyderabad
Assistant Professor of Ophthalmology, Bhaskar Medical College, Yenkapalli, Moinabad, RR district, Telangana
Associate Professor of Ophthalmology, Bhaskar Medical College, Yenkapalli, Moinabad, RR district, Telangana
Associate Professor of Ophthalmology, Bhaskar Medical College, Yenkapalli, Moinabad, RR district, Telangana

Abstract:
Aim: *To study the efficacy of Tacrolimus 0.03% Eye Ointment in the treatment of Refractory Vernal Kerato-Conjunctivitis.*
Materials and Methods: *This is a prospective Observational study of 50 refractory cases of vernal kerato-conjunctivitis of both sexes attending an Ophthalmic OPD of a Tertiary eye care hospital. The cases who do not give consent and those who were allergic to Tacrolimus were excluded from the study. Informed consent was obtained from all cases included in the study. All the cases who did not respond to other modes of treatments were included in the study. Conjunctival scrapping and secretions was taken for staining to look for No. of Eosinophills and Mast Cells. A gap of one week was given after stopping previous treatment. Patients were kept on Carboxy Methyl cellulose Eye drops. Then all patients were given Tacrolimus eye ointment 0.03% for twice daily application in the Lower fornis of both eyes for 4 weeks. Patients were followed up after First, Second and fourth week in order to track reduction of symptoms and resolution of signs. At the end of Fourth week Staining of conjunctival scrapping and secretions was repeated.*
Results: *Of the 100 eyes of 50 cases included in the study, 36 were males and 14 were females. Patients were in the age group of 1-30 years. After first week itching and watering regressed completely, but FB sensation and Discomfort persisted in 5 cases. Signs like Hyperaemia and discharge regressed in all 50 cases. Papillary hypertrophy in 15 cases and Limbal nodule persisted in 15 cases after one week of treatment.*
All symptoms regressed after second week of treatment. Signs like papillary hypertrophy persisted in 10 cases and Limbal Nodule persisted in 10 cases after two weeks.
After four weeks of treatment all symptoms vanished but signs like Papillary Hypertrophy persisted in 5 cases and Limbal nodule remained in 7 cases.
Conclusion: *Effectiveness of Tacrolimus eye ointment 0.03% was seen in more than 90% of the cases which is statistically significant with p value of 0.0001. There was no side effect of Tacrolimus eye ointment as concentration used was 0.03%.*
Key words: *VKC (Vernal Kerato-Conjunctivitis), Tacrolimus, Limbal Tranta's Nodule, Papillary Hypertrophy.*

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I. Introduction:

VKC occurs worldwide but is more frequent in warm, temperate climates. Its highest incidence is seen in Middle East and Mediterranean regions[1]. India also has a high incidence of vernal catarrh[2]. Incidence of vernal catarrh is more in males. Boys are affected twice as frequently as girls. There is an undoubted hereditary influence but direct influence is not established. A family history of atopy is commonly elicited[3].

The condition mostly affects children and young adults and is common in the age group of 5 to 20 years with a peak incidence between 11 to 13 years[3]. The exact role of UV radiation is not clear but there is definite evidence that solar radiation exacerbate the clinical picture in already affected patients[4].

Spring catarrh is seen in following three types[4]:

1. Palpebral form: is characterized by cobble stone papillae on the superior tarsal conjunctiva. The initial change is papillary hypertrophy with connective tissue hyperplasia leading to formation of giant papillae. The papillae are characterized by presence of twigs of blood vessels.
2. Limbal form is characterized by presence of broad, thickened, gelatinous opacification of superior limbus with presence of Horner–Trantas spots (white chalk like dots composed of eosinophils and debris).
3. Mixed form has the features of both palpebral and limbal variety.

The tissue when examined microscopically is infiltrated with lymphocytes, plasma cells, macrophages, basophils and eosinophils. More marked changes are seen in substantia propria of Conjunctiva[5].

Treatment for VKC mainly is avoidance of Allergen and maintaining Lid Hygiene. Medical treatment includes Topical use of Mast cell stabilizers like, Sodium Chromo Glycate[6], Topical Anti Histaminics like Azelastine, Olopatadine, Bepotastine, Alcaftidine[6].

Steroids eye drops like Topical, Dexamethasone, Betamethasone, Prednisolone, Loteprednol and Flouro Metholone(FML)[6] can be used in pulse therapy for one or two weeks and shifting to Anti histaminics and NSAIDS eye drops after that[6].

Immuno modulation can also be done by drugs like Cyclosporine and Tacrolimus which acts by inhibiting Calcineurin and other immune mediators[7].

Tacrolimus (FK 506)[8] 0.03% ointment is a macrolactam derivative with immuno modulatory and anti-inflammatory activity. Produced by the fungus Streptomyces tsukubaensis Tacrolimus Inhibits T-Lymphocyte Activation by binding to an Intracellular protein, FKBP-12 and IL-2 production by binding to an immunophilin and inhibiting the enzymatic activity of calcineurin[8]. Used in concentration of 0.03%.

Peak Tacrolimus blood concentrations ranged from undetectable to 20 ng/mL after single or multiple doses of 0.03%. Plasma protein binding of Tacrolimus is approximately 99% mainly to albumin, alpha-1-acid glycoprotein and has a high level of association with erythrocytes.

Tacrolimus metabolized by oxidase system, primarily the cytochrome P-450 system (CYP3A).

Stinging, burning, soreness, itching, may occur during the first few days of treatment in few individuals. Headache, acne, folliculitis, stomach upset, flu-like symptoms (e.g., fever, chills, runny nose, sore throat, muscle aches). Tacrolimus ointment is contraindicated in patients with a history of hypersensitivity Tacrolimus ointment is stable for 24 months when stored at 25°C (77°F)[8].

Purpose of this study is to see the efficacy of Tacrolimus eye ointment 0.03% in Refractory cases of VKC.

II. Materials and Methods:

This is a prospective Observational study of 100 eyes of 50 refractory cases of Vernal kerato-conjunctivitis of both sexes attending an Ophthalmic OPD of a Tertiary eye care hospital. The cases who do not give consent and those who were allergic to Tacrolimus were excluded from the study. Informed consent obtained from all cases included in the study. There were 36 males and 14 females between the age group of 1-30 years. All the cases who did not respond with Conventional modes of treatments, like Topical NSAIDs, Topical Mast Cells stabilizers, Anti Histaminic eye drops and Topical Steroid were included in the study.

All cases were examined by an experienced Ophthalmologist using Slit Lamp, Snellen's Chart, Direct and indirect Ophthalmoscope.

Conjunctival scrapping and secretions was taken for staining with Lieshman's stain to look for No. Of Eosinophils and Mast Cells. A gap of one week was given after stopping previous treatment. Patients were kept on Carboxy Methyl cellulose Eye drops to wash out previously used drugs. Then all patients were given Tacrolimus eye ointment 0.03% for twice daily application in the Lower fornis of both eyes for 4 weeks. Patients were followed up after First , Second and fourth week for reduction of symptoms and signs. All patients were examined at every follow up visit for Reduction of intensity of Symptoms like Redness, Watering, Itching and FB sensations. They were examined on Slit lamp for regression of signs like, Hyperaemia, Discharge, Papillary Hypertrophy and Tranta's Limbal nodules. At the end of Fourth week Staining of conjunctival scrapping and secretions was repeated.

III. Results and Observations:

50 patients 36 were males and 14 females between age group of 1-30 years. There were 17 cases in 1-10 age group. 31 cases between 11-20 years and 2 cases between 21-30 years.

Before starting treatment with Tacrolimus eye ointment 0.03% ie. 0week all patients had all four symptoms and four signs. At first follow up all patients were relieved of symptoms like Redness, Watering and Itching, only 5 patients had FB sensation.

Regression of signs like Hyperaemia and Discharge was seen in all patients at the end of first week as shown in table2. But 15 cases had Papillary hypertrophy and Tranta's Limbal Nodule after first week of treatment.

On second follow up all 50 patients showed relief from symptoms. As far as Signs are concern, 10 had Papillary Hypertrophy and 10 had Tranta's Limbal Nodules after second week of treatment.

After fourth Week of treatment all cases were relieved of all symptoms. Signs like Hyperaemia and Discharge regressed in all 50 cases, but 5 cases had Papillary hypertrophy and 7 cases had Tranta's Limbal Nodules after four weeks of treatment with Tacrolimus as shown in Table 1 and 2.

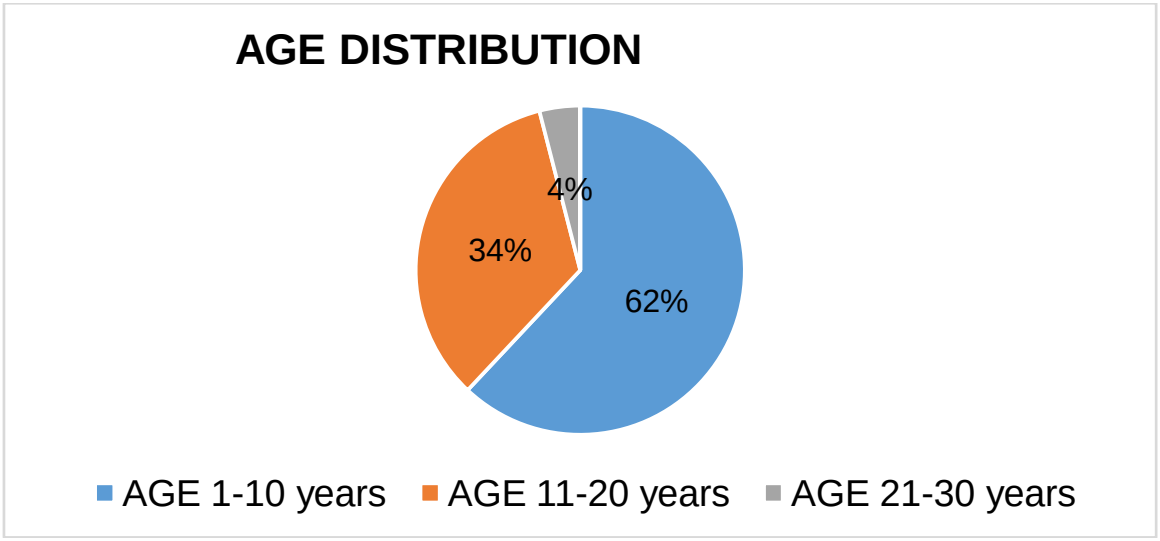

Figure.1 showing number of cases and their age distribution

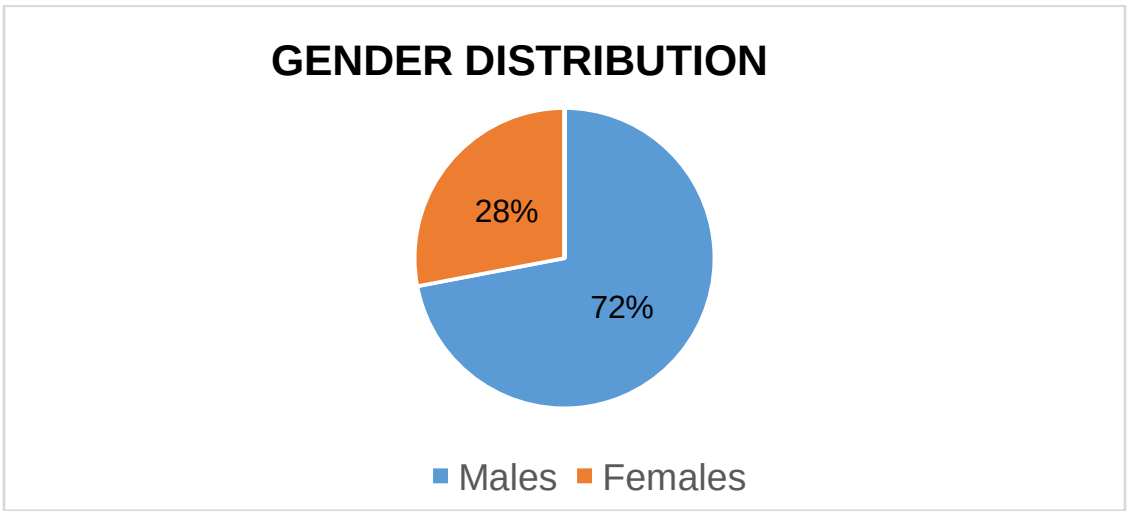

Figure.2 showing Male and Female distribution

Symptoms	0 Week	First Week	Second Week	Fourth week
Redness	50	0	0	0
Itching	50	0	0	0
Watering	50	0	0	0
FB sensation	50	5	0	0

Table 1:No. of cases with symptoms at the end of week mentioned (P value 0.0001)

Signs	0 Week	First Week	Second Week	Fourth Week
Hyperaemia	50	0	0	0
Discharge	50	0	0	0
Papillary hypertrophy	50	15	10	5
Tranta's Limbal Nodule	50	15	10	7

Table 2: No. of cases with signs at the end of week mentioned (P value of 0.001)

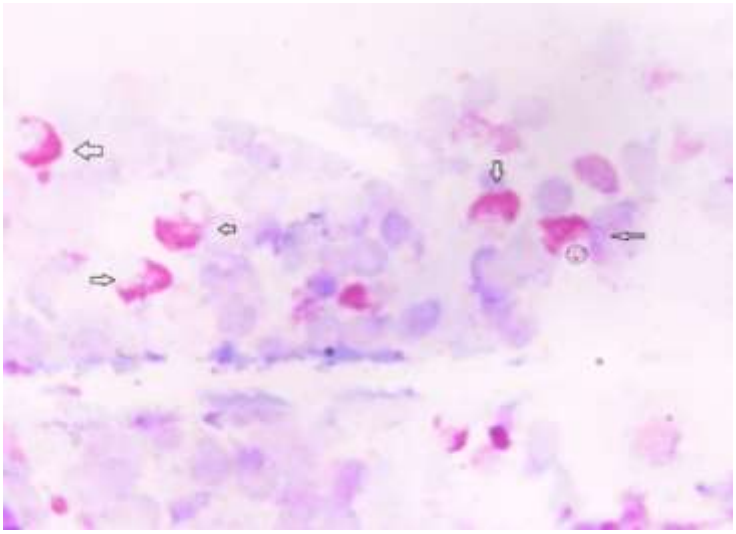

Figure 3 showing Cytology of Conjunctival scrapping. Arrow showing Eosinophils and Mast cells along with epithelial cells

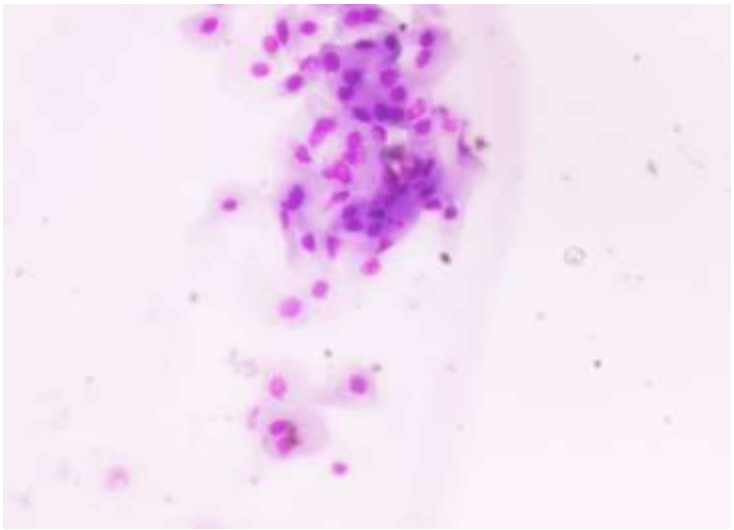

Figure 4 showing absence of Eosinophils and Mast cells. Only Coniunctival epithelium seen after 4 weeks of treatment with Tacrolimus

Figure 5: Tranta's Limbal Nodules Figure 6: Resolution of Limbal nodule after Treatment with Tacrolimus

Figure 7 showing Cobblestone Papillae

Figure 8 showing resolution of Papillae after Treatment with Tacrolimus

IV. Discussion:

Abdur Rahman M Al Amri[9] et al study 40 eyes of 20 patients of VKC with Tacrolimus 0.1% eye ointment applied twice dail for 4 weeks and then tapered to once daily for another month found it effective and safe. Symptoms like watering, Redness and FBS got relieved after 2 weeks. Whereas Signs like Hyperaemia, discharge got regressed after two weeks. Signs like Papillary Hypertrophy took 4 weeks to resolve. Trantas spot remain in 6 off 20 patients. This is in consistent with present study.

Navin Chandra et al[10] studied 40 eyes of 20 patients of VKC treated with 0.1% Tacrolimus eye ointment showed total relief from symptoms and signs after twice daily usage of drug. This is also consistent with present study wherein we got total recovery after 4 weeks of usage.

Mahmood Eltagoury et al[11] studied 50 patients of VKC treated with Tacrolimus 0.03% eye ointment twice daily application for 3 months ie 12 weeks. All symptoms and signs got resolved after 12 weeks with statistical significance of 0.005 on all signs and symptoms. This is in consistent with our results which we achieved with four weeks usage of drug.

Sandra Flavia , Darakhshanda Khurrum et al[12] studied 10 Children of Refractory VKC with Tacrolimus 0,03% eye ointment . They found it effective and safe for usage in Children. In present study we had 48 patients below 20 years of age. They also achieved drastic resolution in Symptoms and signs after 4 weeks of usage.

Bhavesh et al[13] studied different concentration of Tacrolimus ie. 0.1% and 0.03% eye ointments and found both effective. Their conclusion was).03% is safe and equally effective.

Sameera Irfan et al[14] studied 54 cases of refractory VKC with 0.03% skin ointment twice daily application for 4 weeks and found it to be effective in relieving signs and symptoms. In present study we used 0.03% Tacrolimus eye ointment and got same results.

Al Khaikhah et al[15,] , Moscovici et al[16] used Tacrolimus eye drops 0.03% and got same results as in present study.

Yuichi Ohashi et al[17] studied 56 patients of VKC with Tacrolimus Eye suspension 0.5% twice daily and got resolution of signs and Symptoms within 4 weeks which is consistent with Present study.

V. Conclusion:

Tacrolimus 0.03% eye ointment is effective in resolving Signs and Symptoms within 2 weeks. Even Refractory Signs like papillary hypertrophy anf Tranta's Limbal Nodules get resolved in 85-90% of patients after 4 weeks twice daily usage of drug. It is also safe both in adults and Children.

Institutional Ethics Committee approval Obtained for this study
Financial interest : Nil
Conflict of interest : None

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