Original Article

Effectiveness of Supratarsal Injection of Bevacizumab in the Treatment of Vernal Kerato Conjunctivitis

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ABSTRACT

Purpose: To evaluate the effectiveness of supratarsal injection of Bevacizumab in the treatment of Vernal Kerato-conjunctivitis (VKC).

Study Design: Quasi experimental study.

Place and Duration of Study: LRBT Karachi from September 2022 to September 2023.

Methods: This study included 110 eyes of 60 patients with VKC and divided into two groups by convenient sampling. In one group (n=30) 0.1ml of Bevacizumab 2.5%was injected in supratarsal space with 27-gauge needle under topical anaesthesia. Other group (n=30) received conventional treatment. The sign and symptoms were checked at one week and at one month in all patients. The qualitative variables were presented as frequency and percentage while quantitative variables were shown as mean ± standard deviation. Chi square test was applied for comparison.

Results: Mean age of the patients was 12.4 +1.9 years. There were 46 (76.0%) males. Itching and photophobia was not seen in 50% of the patients treated with Bevacizumab while this percentage was 13.3% and 10% respectively in case of conventional treatment. Similarly, redness, discharge and limbal papillae were not seen in 70%, 73.3% and 83.3% respectively after Bevacizumab application. While it was 16.6%, 30% and 10% respectively after conventional treatment. Significant improvement in itching, photophobia, redness, discharge and limbal papilla was observed in the group of patients who received supratarsal Bevacizumab injection as compared to those who received conventional treatment ($p<0.05$).

Conclusion: Bevacizumab is a safe and effective treatment in patients of VKC refractory to conventional treatment.

Key Words: Vernal Kerato-conjunctivitis, Bevacizumab, Atopic conjunctivitis, Papillae.

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INTRODUCTION

Allergic conjunctivitis includes acute allergic conjunctivitis, seasonal and perennial conjunctivitis, atopic conjunctivitis and vernal conjunctivitis.[1] Vernal kerato-conjunctivitis (VKC)is a bilateral, recurrent condition usually affecting boys. It is common in warm dry climates. Atopic kerato-conjunctivitis (AKC)and VKC are two severe forms of allergic conjunctivitis, as they are concerned with more severe ocular complications such as corneal scarring and keratoconus.[2,3] If the cornea is affected, symptoms and visual impairment could happen. Three types of VKC have been described; tarsal (palpebral), limbal (bulbar), and mixed type, depending on the major conjunctival district affected.[4] Large papillae (>1 mm) in the first kind, which is more common in Europe and

the Americas, are primarily found at the upper tarsus. Those that are 7-8 mm in size are referred to as cobblestone papillae and are made of proteoglycans and collagen types I and II that are part of the vasculostromal structure. Horner-Trantas nodules and limbal infiltrates are typically found with the limbal form, which is more common in Africa; the mixed type has traits that are in between the two.[5]

Due to the its effects on quality of life and potentially blinding sequel (shield ulcers, keratoconus, limbal stem cell shortage, irregular astigmatism), treatment of this pathology is crucial.[6] Despite some suggestions, there is disagreement on treatment approaches. Treatments such as cleaning the eyes, shielding oneself from the sun and eliminating allergens that have caused sensitization are non-pharmacological therapies. Artificial tears, mast cell stabilisers and antihistamines are frequently used. Eye drops containing corticosteroids are administered in cases of crisis or uncontrolled VKC. Although they have a strong impact, they can have major adverse effects like cataracts and glaucoma, which is why calcineurin inhibitors like cyclosporine are used.[7]Signs and symptoms of VKC include hyperemia, keratitis, tarsal papillae, limbal papillae, itching, photophobia, discharge, tearing and foreign body feeling.[8]

Thus, the goal of this study was to evaluate the effectiveness of supratarsal Bevacizumab on VKC and compare with conventional therapy.

METHODS

This Quasi experimental study was conducted at LRBT Karachi from September 2022 to September 2023. In this study 60 patients of VKC were divided into two groups. One group (n=30) received conventional therapy including antihistamines, mast cell stabilisers, dual-acting agents and artificial tears. Other group (n=30) received supratarsal Bevacizumab 2.5%. Both genders were included and the age range of the study participants was from 8 to 16 years. An informed consent was obtained from each participant or their parents prior to the study.

The conjunctiva of the patient was anaesthetized with Propracaine 0.5% eye drops. 1ml syringe of Bevacizumab 2.5% was used. Of which 0.1 ml was injected using a 27-gauge needle into the supratasal space of the upper eyelid as part of the medical therapy. Follow up was done at one week and one month post injection.

RESULTS

A total of 120 eyes of 60 patients were treated. Mean age was 12.4 + 1.9 years. There were male predominance with 46 (76.0%) boys. Table 2 shows the effect of supratarsal Bevacizumab injection and conventional treatment for VKC at one week. It was observed that itching and photophobia was not seen in 50% of the patients treated with Bevacizumab while this percentage was 13.3% and 10 % respectively in case of conventional treatment. Similarly, redness, discharge and limbal papillae were not seen in 70%, 73.3% and 83.3% respectively after Bevacizumab application. While the improvement in these sign and symptoms were seen in 16.6%, 30% and 10% respectively after conventional treatment. Significant improvement in itching, photophobia, redness, discharge and limbal papilla was observed in the group of patients who received supratarsal Bevacizumab injection as compared to those who received conventional treatment ($p<0.05$).

Table 2 presents a comparison between the outcomes of conventional therapy for VKC after one month and supratarsal Bevacizumab injection. Notably, the results indicate a complete elimination of signs and symptoms of VKC in 100% of patients treated with Bevacizumab. In contrast, among patients

Table 1: *Comparison of Bevacizumab with Conventional Treatment regarding sign and symptoms of VKC at one week.*

Signs and Symptoms	Conventional Treatment (n=30)		Supratarsal Injection of Bevacizumab (n=30)		p-value
	Yes Frequency (%)	No Frequency (%)	Yes Frequency (%)	No Frequency (%)	
Itching	26 (86.7%)	4 (13.3)	15 (50)	15 (50)	0.002
Photophobia	27 (90)	3 (10)	15 (50)	15 (50)	0.001
Redness	25 (83.3)	3 (16.6)	9 (30)	21 (70)	0.000
Discharge	21(70)	9 (30)	8 (26.6)	22 (73.3)	0.000
Limbal papillae	27 (90)	3 (10)	5 (16.7)	25 (83.3)	0.000

Chi Square test was applied for comparison and $p<0.05$ was considered significant

Table 2: *Comparison of Bevacizumab with Conventional Treatment regarding sign and symptoms of VKC at one month*

Signs and Symptoms	Conventional Treatment (n=30)		Supratarsal Injection of Bevacizumab (n=30)		p-value
	Yes Frequency (%)	No Frequency (%)	Yes Frequency (%)	No Frequency (%)	
Itching	20 (66.6)	10 (33.3)	0(0.0)	30 (100)	0.000
Photophobia	16 (53.3)	14 (46.7)	0(0.0)	30 (100)	0.000
Redness	19 (63.3)	11 (36.7)	0(0.0)	30 (100)	0.000
Discharge	14(46.7)	16(53.3)	0(0.0)	30 (100)	0.000
Limbal papillae	11 (36.7)	19 (63.3)	0(0.0)	30 (100)	0.000

Chi Square test was applied for comparison
$p<0.05$ was considered significant

who underwent conventional treatment, 33.3% did not experience itching, 46.7% did not report photophobia, 36.7% showed no signs of redness, 53.3% did not exhibit discharge and 63.3% did not display limbal papillae.

DISCUSSION

VKC is a persistent inflammatory condition affecting the ocular surface, representing one of the most severe forms of allergic conjunctivitis. Given its chronic nature, it has the potential to harm cornea, leading to serious complications that can jeopardize vision if not addressed.[9] Typically, this condition primarily impacts young children, with onset occurring around the age of 7 years.[10]

Arlt is credited with presenting the first evidence of VKC when he reported three instances of peri-limbal edema in juvenile patients in 1846. Later, the limbal white spots that Horner had previously shown were characterised by Trantas in 1899. Gabrielides discovered eosinophils in the peripheral blood and conjunctival secretions of VKC patients in 1908. Trantas described the range of corneal alterations observed in VKC in 1910.[11]

VKC is a bilateral allergic condition that usually affects boys and occurs in hot, dry climates. The increased frequency in hot climates is speculated secondary to pollens and other allergens. Personal or family history of atopy or any kind of allergy is seen in this condition. It was previously thought to be exclusively caused by IgE-mediated mast cell discharge but now it is believed that it is not solely due to mast cells but also due to eosinophil that are seen in majority of the conjunctival scrapings. Although no direct genetic correlations have been found, a hereditary relationship has been proposed.[12]

Initial symptoms such as itching, watering, photophobia, redness can be treated with topical medicines such as antihistamines, mast cell stabilizers, mild steroids and artificial tears. Severe symptoms of VKC are extremely disturbing leading to corneal scaring and irregular astigmatism. Oral corticosteroids can be given in life threatening cases, Immunomodulator and tacrolimus is used as steroid sparing agents. Vascular endothelial growth factor, or VEGF, levels in blood samples and tear films from VKC patients have been measured in previous study.[13]

Inflammatory cells such as fibroblasts, epithelial cells, mast cells are responsible for VEGF in VKC. Leukocyte extravasation is brought on by matrix metalloproteases (MMPs) via limited proteolysis of basement membranes, proteoglycan, laminin, fibronectin, and collagen degradation, and activation of precursor forms of additional MMPs. The pathophysiology of conjunctival inflammation, remodelling, and corneal alterations in VKC is likely also influenced by an imbalance between MMPs and their natural tissue inhibitors (TIMP). Actually, all types of active VKC have high expression levels of MMP-1, MMP-2, MMP-3, MMP-8, MMP-9, and MMP-10. This leads to a rise in proinflammatory cytokines such IL-1b and tumour necrosis factor-α (TNF-α). Treatment for anterior segment eye illness, particularly when VEGF levels are elevated in corneal neovascularization, may benefit from anti-VEGF medication.[14]

Results of our study are consistent with the previous reports that showed higher prevalence of VKC among boys than girls.[15,16]Moreover, the mean age of the study participants was 12.4 ±1.9 years. This was presented in the literature that VKC generally affects young boys and may resolve till adolescence.[17]

In earlier studies, the management of VKC

involved the use of immunosuppressant such as tacrolimus dermatological ointment at 0.1%,[18] or steroid drops.[19] Previously Non-Steroidal Anti-Inflammatory Drugs (NSAID) were also used for the management of VKC.[20] However, it was noted that achieving a complete resolution of signs and symptoms was not attained in 100% of cases with these treatments. The present study outcome shows that at one week itching and photophobia was resolved in 50% of the patients and redness, discharge and limbal papillae were not seen in 70%, 73.3% and 83.3% respectively after Bevacizumab application (Table 1). Moreover, complete elimination of signs and symptoms of VKC in 100% of patients treated with Bevacizumab at month was observed (Table 2). This improvement in sign and symptoms of VKC was significantly different with the patients who received conventional treatments ($p<0.05$). Bevacizumab has not previously been documented in any studies as a therapy for VKC. The ophthalmologist's clinical judgement and the patient's satisfaction were key elements in these results.

While this study provides valuable insights on the treatment of refractory VKC, it has certain limitations: The study included a relatively small sample size of 60 patients with short Follow-up. The use of convenient sampling may introduce selection bias, as it may not adequately represent the entire population of VKC patients. Conducting the study in a single center may limit the generalizability of the findings to other populations or settings. The study primarily focused on efficacy outcomes, and while there were no reported adverse events, the safety profile of Bevacizumab in VKC warrants further investigation, especially considering its off-label use in ophthalmology. Addressing these limitations in future research would strengthen the evidence base and provide a clearer understanding of the role of Bevacizumab in VKC management.

CONCLUSION

Although the evidence supporting the use of Bevacizumab for VKC is not extensive, and its safety and efficacy profile in this context is not fully established, however, it can be considered in refractory cases. Further research, including well-designed clinical trials, is needed to better understand the role of Bevacizumab in VKC treatment.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(LRBT/TTEC/ERC/4611/11).**

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Authors Designation and Contribution

Zeeshan Kamil; Chief Medical Officer & Senior Consultant Ophthalmologist: *Concepts, Design, Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Fatima Ahmed; Associate Ophthalmologist: *Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Saliha Naz; Assistant Professor & Senior Consultant Ophthalmologist: *Manuscript editing, Manuscript review.*

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