

Outcome of the use of topical bevacizumab in treatment of superficial corneal vascularization due to pterygium.

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Abstract

Purpose: To evaluate the results of using topical bevacizumab (Avastin) as a treatment of superficial corneal vascularization due to pterygium.

Methods: This study was a prospective interventional study. Total thirty patients were included in this study. All were diagnosed with superficial corneal vascularization due to pterygium. Careful history was taken from all patients and they underwent ophthalmological examination including best corrected visual acuity (BCVA), slit lamp biomicroscopy examination and color photos of the ocular surface (cornea and conjunctiva). They received bevacizumab topical eye drops with a concentration of 0.5 mg/ml four times daily for two weeks. Study appointments were held during weeks 1, 2, 6, 12 and 24. This study was conducted at Zagazig ophthalmology hospital.

Results: There was highly significant difference in the superficial corneal vascularization after one and two weeks. Moderate response increases from the first to the second week (3.3% vs. 56.7% respectively, $P < 0.001$). The BCVA improved in about one third of the studied group (33.3%) and there was no significant difference in the corneal opacity before and after treatment. Only four eyes (4/30; 13.3%) showed decrease in the corneal opacity. No adverse events ascribed to the treatment were noted.

Conclusion: The use of topical bevacizumab eye drops in cases of pterygium with superficial corneal vascularization is safe, well tolerated, associated with mild to moderate regression of superficial corneal vascularization and not associated by any drug related side effects.

Keywords: Corneal vascularization, Pterygium, Bevacizumab, Angiogenic privilege, Angiogenesis.

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Introduction

The normal cornea is devoid of both blood and lymphatic vessels and actively maintains that avascularity. This is called corneal "angiogenic privilege" that is essential for corneal transparency and vision [1]. Superficial corneal vascularization is characterized by the creeping of new blood vessels into the cornea from the limbus due to many inflammatory, infectious, degenerative, or traumatic disorders. This dangerous complication occurs when the balance between angiogenic and anti-angiogenic elements is directed towards angiogenic molecules [2].

The Vascular endothelial growth factor (VEGF) is an essential mediator of retinal and iris neovascularization after injury, ischemia and in diabetic retinopathy too. Corneal epithelial and endothelial cells, vascular endothelial cells of limbal vessels, and fibroblasts and macrophages in scar tissue all excrete VEGF, specifically in inflamed and vascularized corneas. The receptors of VEGF (VEGFR1 and VEGFR2) are also found in newly proliferating vascular endothelial cells in inflamed cornea [3].

It is suggested that VEGF inhibition may be an effective therapeutic modality for superficial corneal vascularization [4]. Bevacizumab is a humanized monoclonal antibody that binds to isoforms of VEGF1. It was initially approved for the

treatment of metastatic colorectal cancer; however, it has since been used to treat a variety of ophthalmic conditions.

The route of administration that provides the best combination of safety, efficacy, and practicality should be pursued; with regard to the cornea, the preferred method of administration is generally ocular surface topical instillation [4].

Subjects and Methods

This study was a prospective interventional study that was conducted at Zagazig Ophthalmology Hospital. Informed consent was obtained from all patients before administration of the treatment including their acceptance to use it, know the advantages, disadvantages, risks, possible complications and periodical follow up for 24 weeks.

Thirty patients (12 females and 18 males) with only one eye of each of them were admitted to this study. All of them were among 15 to 70 years old with acquired superficial corneal vascularization due to pterygium and previous adequate visual acuity. None of them was cardiac or hypertensive and they all had a cornea and conjunctive with no active inflammation, infection or ulcers. Patients with no light perception and pregnant females were excluded.

All patients were subjected to history taking including personal history (name, age, gender, occupation, and residence), complaint, present history and past history especially ophthalmic history including history of corneal infection, inflammation, degenerative disorders and traumatic disorders.

They underwent Ophthalmological examination including assessment of the visual acuity using "Landolt's chart" and Slit lamp bio microscopy examination to determine the type and the cause of superficial corneal vascularization and to take corneal photos for follow up.

Technique of Usage

Method of preparation

Bevacizumab eye drops were prepared in the hospital pharmacy under complete sterile condition from the standard solution diluted in 0.9% saline to a concentration of 0.5 mg/ml. The eye drops were stored at 4°C during that time.

Method of administration

The patients were instructed to instill 1 drop 4 times daily for 2 weeks. They were also instructed to maintain punctual occlusion and close their eyes for at least 1 min after drug instillation in order to reduce systemic drug absorption. The patients who were using other ocular drops were instructed to instill the bevacizumab drops first and wait at least 5 min before instilling other drops (if the patients were already on other medical ophthalmic drops) in order to prevent drug washout.

Follow up Protocol

Follow-up evaluations were performed during weeks 1 and 2 and they included BCVA as well as slit-lamp examinations to determine the type of the corneal vessels either superficial or deep and to detect regression of the vessels either mild which is defined as partial regression of the superficial corneal vascularization or moderate which is defined as clear-cut regression of superficial corneal vascularization. Also, color photos of the ocular surface (cornea and conjunctiva) were obtained. During the follow up visits at weeks 6, 12 and 24, only slit lamp examination were done to exclude recurrence and complications.

Results

Thirty eyes of 30 patients (12 females and 18 males) were included in this study. The mean age of the subjects was 52.6 (SD 13.4) and ranged from 28 to 70 years (Table 1).

Table 1. Socio-demographic data of the studied group.

Variable	Studied group (n=30)
Age	
Mean ± SD	52.6 ± 13.4
Range	28 – 70

	No.	%
Gender		
Female	12	40
Male	18	60

The BCVA improved in about one third of the studied group (33.3%), however the remaining 66.7% didn't show any change at all (Table 2).

Table 2. Effect of Avastin on the (BCVA) of the studied group.

Variable	Studied group (n=30)	
	No.	%
BCVA		
Unchanged	20	66.7
Improved	10	33.3

But there was highly significant (HS) ($P < 0.001$) difference between the studied group as regarding effect of Avastin on superficial corneal vascularization after one and two weeks. It was noticed that moderate response increases from the first to the second week (3.3% vs. 56.7% respectively) (Table 3).

Table 3. Effect of Avastin on superficial corneal vascularization after one and two weeks among the studied group.

Variable	One week (n=30)		Two weeks (n=30)		Test χ^2	P value
	No.	%	No.	%		
Superficial Corneal vascularization						
No response	10	33.3	8	24.6	22.61	<0.001 (HS)
Mild	19	63.3	5	16.7		
Moderate	1	3.3	17	56.7		

Also, the corneal opacity decreased in 13.3% of the studied group, however the remaining 86.7% didn't show any change at all (Table 4).

Table 4. Effect of Avastin on corneal opacity of the studied group.

Variable	Studied group (n=30)	
	No.	%
Corneal opacity		
No change	26	86.7
Decreased	4	13.3

Discussion

Superficial corneal vascularization represents a challenging clinical condition that may also lead to significant visual impairment. Current therapies aiming to induce the regression

of corneal vessels are not uniformly effective and are variably associated with undesirable side-effects.

Several VEGF inhibitors are currently used for the treatment of neovascular age-related macular degeneration and macular edema. Several studies have evaluated the application of topical bevacizumab in cases of superficial corneal vascularization, at different concentrations [5].

As regarding the BCVA, in this study nine eyes (9/30; 33.3%) showed improvement of the BCVA after receiving the treatment and that was consistent with the results of other studies. Waisbourd et al. [6] reported improvement of BCVA in nine eyes (9/17; 52.9%) using topical bevacizumab eye drops with a concentration 25 mg/ml four times daily for two weeks. Krizova et al. [7] reported improvement of BCVA after receiving topical bevacizumab eye drops with a concentration of 2.5 mg/ml twice daily for 2 weeks.

Regarding the regression of the superficial corneal vascularization, in this study there was highly significant difference between the studied groups after one and two weeks follow up after receiving treatment (Figure 1). It was noticed that moderate response increased from the first to second week (1/30; 3.3% vs. 17/30; 56.7%). Also, other studies reported regression of the superficial corneal vessels.

Waisbourd et al. [6] reported regression of the superficial vessels in eleven eyes (11/17; 65%). Ferrari et al. [5] reported regression of the superficial corneal vascular area in 55.3% of the studied eyes at the end of third week of treatment.

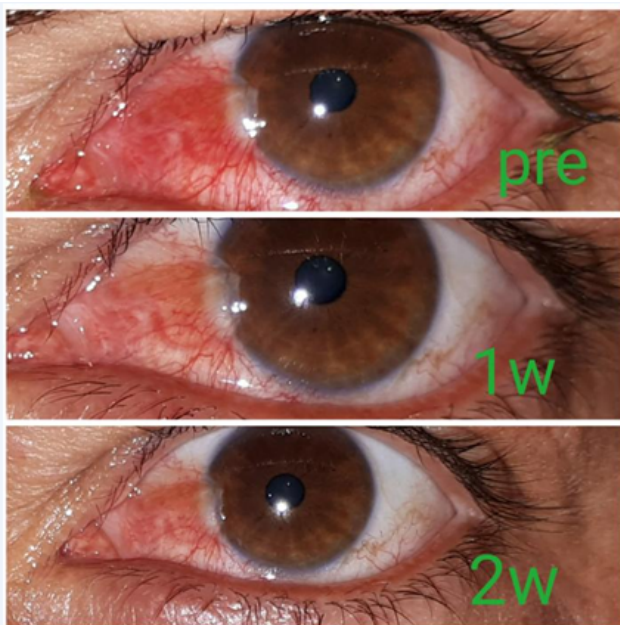


Figure 1. Pre, one and two weeks after treatment of a case of pterygium with mild regression.

Regarding the corneal opacity, No significant difference was reported before and after treatment in this study. Only four eyes (4/30;13.3%) showed decrease in the corneal opacity (Figure 2). While Cheng et al. [8] reported reduction of the opacity in 20% of studied eyes after receiving topical bevacizumab eye drops with a concentration of 10 mg/ml four

times daily for 3 weeks. Ferrari et al. [5] showed no significant change in the corneal opacity after treatment.

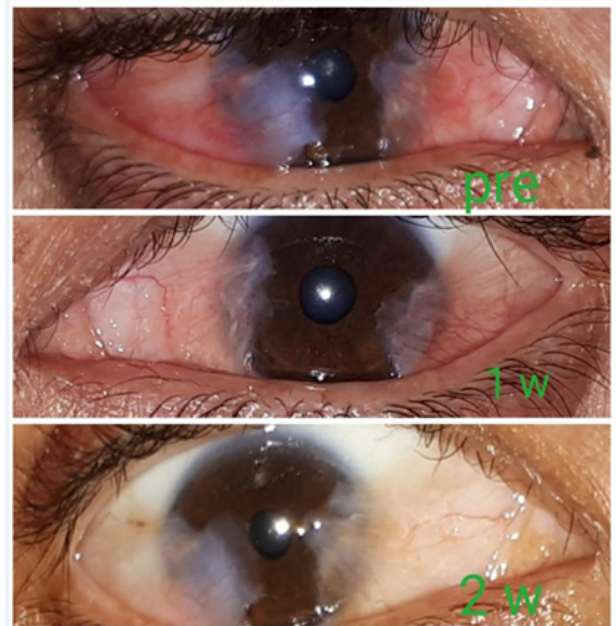


Figure 2. Pre, one and two weeks after treatment of a case of pterygium with moderate regression.

Regarding complications, neither systemic nor local complications were detected in this study but Waisbourd et al. [6] reported local complications in the form of one case each of epitheliopathy, eye lid swelling and chalazion and these complications were found to be mild and transient and the authors explained them due to the use of high dose of topical bevacizumab eye drops. Fallah et al. [9] has not mention any local or systemic adverse effects among their patients who received bevacizumab topical eye drops with a concentration of 1-5 mg/ml.

Conclusion

In summary, that the use of topical bevacizumab (avastin) eye drops in cases of superficial corneal vascularization due to pterygium is safe, well tolerated, associated with mild to moderate regression of superficial corneal vessels and not associated by any drug related side effects. Further clinical and experimental studies with more patients and longer follow up are needed to improve the safety and predictability and to ensure the stability of results.

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