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To Evaluate Functional Efficacy of Subconjunctival Bevacizumab in Cases of Corneal Neovascularization

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Abstract

Background: To evaluate functional efficacy of subconjunctival bevacizumab in cases of corneal neovascularization

Design: Prospective comparative study

Material & Methods: Fifty cases of corneal NV who are relatively resistant to all conventional modes of medical and surgical management were included in this prospective study conducted in our OPD. The conventional modes of medical treatment was more than 6 weeks of non-steroidal anti-inflammatory drugs and low potency steroids. A standard clinical proforma was filled in all cases for analytical study which included visual acuity recording, pre-injection digital photograph, recording of corneal vessel extent and diameter. All patients underwent subconjunctival bevacizumab 1.25mg (0.05 ml) under topical medication close to the corneal limbus near the corneal NV. The patients were followed up after 2 weeks and then again after 6 weeks.

Results: The study of vessel extent showed that the vessels had regressed completely in 3 cases, while only marginal reduction in grades of vessel extent was seen in other categories (statistically significant p=0.000).The analysis of the vessel diameter and inflammation revealed that there was complete reduction of vessel in 3 cases, however only marginal reduction in grades of vessel diameter and inflammation was seen in other categories (statistically significant p=0.000). Analysis of visual acuity showed only marginal improvement in 7 cases out of 50(statistically significant p=0.000).

Conclusions: This study concludes that subconjunctival bevacizumab (anti-VEGF agent) is a new and effective modality of reducing the corneal vascularization

Keywords: Subconjunctival bevacizumab, Corneal vascularization

Introduction

The development of new blood vessels in the cornea, called neovascularization(NV) occurs as a result of disequilibrium between angiogenic and antiangiogenic stimuli[1,2]. Corneal angiogenic factors include Vascular Endothelial Growth Factor(VEGF),[2,3] with studies showing that VEGF activation can induce corneal NV, and that inhibition of VEGF can block new vessel formation in human and animal cornea model[3,4].This corneal NV may lead to severe impairment of vision.

Until now, the most common course of treatment for anti-angiogenic therapy in the cornea was nonspecific anti-inflammatory drugs and sometimes anti-angiogenic steroids, but they were often unable to prevent or stop neovascularization[1,2,5-9]. Even surgical treatment with corneal transplantation frequently failed, as the new vessels induced an inflammatory rejection of the graft. However, the rapid progress in angiogenesis research in the last few years has led to the development of several novel, specific anti-angiogenic drugs for use in both oncology and ophthalmology.

Bevacizumab is a full-length recombinant humanized murine monoclonal antibody that binds to and inhibits the biological activity of

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all five human VEGF-A isoforms: VEGF115, VEGF121, VEGF165, VEGF189, and VEGF206. It prevents VEGF-A from ligating to its endothelial receptors, VEGFR-1 and VEGFR-2, but does not neutralize other members of the VEGF gene family, such as VEGF-B or VEGF-C. The antibody was engineered by assembling VEGF-A binding residues from the murine-neutralizing antibody into the framework of a human immunoglobulin. Bevacizumab has been approved by the US Food and Drug Administration for use in the treatment of metastatic colorectal cancer.

Since mid-2005, it has been applied off-label in the treatment of ocular disease and has shown promising short-term results in alleviating intraocular neovascular conditions. Bevacizumab has also been a valuable addition to the limited treatment options available for age-related macular degeneration. Encouraging results for intravitreal bevacizumab treatment for age-related macular degeneration have led to trials involving macular edema in central vein occlusion, iris NV, and subsequently, severe proliferative diabetic retinopathy[9,10,11]. Such trials have encouraged investigations on the use of topical bevacizumab for corneal NV.

Reports that the systemic application of bevacizumab in animal models inhibited inflammatory corneal neovascularization[5,6] led to the assumption that bevacizumab might also be clinically beneficial in patients who do not respond to conventional steroid therapy. This was followed by successful experiences with bevacizumab applied as eye drops[7,8,9] or subconjunctival[10,11,12] in patients with progressive corneal neovascularization. Topical treatment was found to be safe and efficient, without local or systemic adverse effects[13,14] some authors suggested that it could serve as a pre-transplantation treatment option[15].

Further studies reported a reduction in corneal inflammation and choroidal neovascularization after subconjunctival injection of bevacizumab, and a reduction in neovascular glaucoma after intracameral injection. Intravitreal injection is currently the most common route of treatment for age-related macular degeneration with choroidal NV.This study has been taken to study this anti VEGF property of bevacizumab to reduce the corneal vascularization following any ocular pathology.

Material & Methods

The patients were selected from those attending the OPD between Apr 2011 and Oct 2011. 50 patients of corneal neovascularization were selected for this treatment modality. Fifty cases of corneal NV who are relatively resistant to all conventional modes of medical and surgical management were included in this prospective study conducted in our OPD. The conventional modes of medical treatment was more than 6 weeks of non-steroidal anti-inflammatory drugs and low potency steroids.

A standard clinical proforma was filled in all cases for analytical study which included visual acuity recording, pre-injection digital photograph, recording of corneal vessel extent and diameter. All patients underwent subconjunctival bevacizumab 1.25mg (0.05 ml) under topical medication close to the corneal limbus near the corneal NV.

The patients were followed up after 2 weeks and then again after 6 weeks. Detailed ocular examination was done including visual acuity recording, digital photograph, recording of corneal vessel extent and diameter. The results were compiled and analyzed at the end of study.

Results

Age distribution showed that the maximum number of cases were in the age group 51-60 yrs (16 cases) while 15 cases were in the 41-50 yrs age group, 11 in 31-40 yrs and 8 in 21-30 yrs age group.

The study of vessel extent showed that the vessels had regressed completely in 3 cases, while only marginal reduction in grades of vessel extent was seen in other categories. [photo1] By Chi square test, the result was significant(p=0.000) and by Wilcoxon signed Ranks test for comparison between pre-treatment and post-treatment the Z value was -3.464 and p=0.001 which was significant. [Table 1]

The analysis of the vessel diameter and inflammation revealed that there was complete reduction of vessel in 3 cases, however only marginal reduction in grades of vessel diameter and inflammation was seen in other categories [Table 2]. By Chi square test, the result was significant (p=0.000) and by Wilcoxon signed Ranks test for comparison between pre-treatment and post-treatment the Z value was -2.236 and p=0.025 which was significant.

Table 1: Vessel extent pre and post subconjunctival bevacizumab (after 6 weeks) of single injection of bevacizumab.

Vessel Extent		Pre-treatment	Post-treatment
Grade	**Description**		
0	No vessel over limbus	0	3
1	vessel over corneal limbus or covering 0-25% area	13	15
2	vessel covering 25-50%	16	14
3	vessel covering 50-75 %	14	12
4	vessel covering entire area	7	6
Total		**50**	**50**

Table 2: Inflammation or diameter of Vessels pre and post subconjunctival bevacizumab (after 6 weeks) of single injection of bevacizumab.

Inflammation or diameter of Vessels		Pre-treatment	Post-treatment
Grade	**Description**		
0	No inflammation	0	3
1	Mild inflammation or vessel of small diameter	17	14
2	Moderate inflammation or vessel of medium diameter	19	21
3	Moderate inflammation or vessel of large diameter	14	12
Total		**50**	**50**

Table 3: Visual acuity pre and post subconjunctival bevacizumab.

Visual acuity	Pre- treatment	Post- treatment
6/6-6/12	1	1
6/18- 6/24	8	10
6/36-6/60	13	16
<6/60	28	23
Total	**50**	**50**

Analysis of visual acuity showed only marginal improvement in 7 cases out of 50.[Table 3] By Pearson Chi square test, the result was significant(p=0.000) however by Wilcoxon signed Ranks test for comparison between pre-treatment and post-treatment the Z value was -1.993 and p=0.053 which was not significant.

The reduction of vessel extent, vessel diameter and inflammation was statistically significantly. However commensurate reduction in visual acuity was not statistically significant. Unlike the intravitreal mode of injection, where the effect is seen to wear of in 4-6 weeks, the effect on corneal vascularization was seen to be more longlasting in cases which showed good resolution, (in 3 cases with a follow up of 2-6 months).

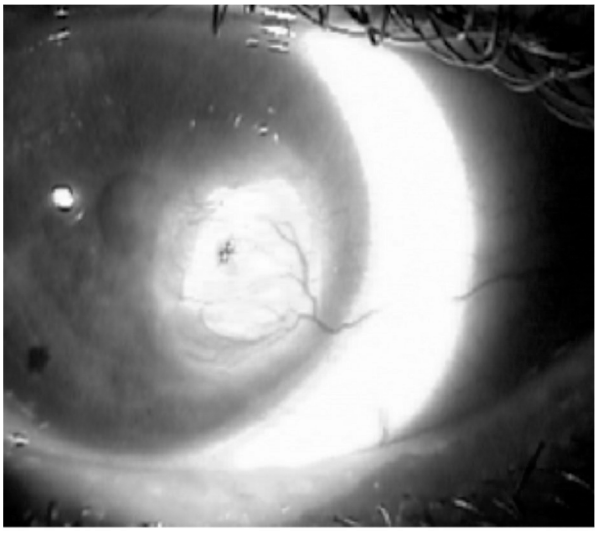

Fig. 1 Regression of vascularization from central visual axis 2 weeks after bevacizumab injection

Discussion

The renewed interest in angiogenesis in various ocular pathologies and its inhibition by anti-angiogenesis agents has accelerated the research in both molecular mechanisms of angiogenesis and antiangiogenesis. Corneal neovascularization due to various causes like infections (bacterial, viral or fungal), trauma (particularly burns), trachoma and contact lens wear is a seemingly untreatable condition. New vessels cause structural changes that allow the overflow of fluid to the extravasculature, blood stasis and hemorrhage, and they can reduce corneal transparency with subsequent and progressive vision impairment. Corneal neovascularization is one of the greatest risk factors for corneal transplant rejection[2] because it allows leukocytes access to donor tissue antigens[16,17].

The first-line treatment for corneal neovascular diseases remains corticosteroids because of their ability to reduce the inflammatory process and vascular proliferation, both of which are initiated soon after the ocular trauma. However, side effects related to the non-specificity of corticosteroids limits their use. Such side-effects include the increased risk of cataracts and glaucoma due to high intra-ocular pressure (IOP). Non-steroidal anti-inflammatory drugs like flurbiprofen and ketorolac are also used with minimal success. Various modalities have been tried and studied for reducing this corneal vascularization which include laser photocoagulation of feeder vessels, inhibition of angiogenesis with cyclosporine A, methotrexate,

doxycycline, triamcinolone, indomethacin, rapamycin, low-molecular-weight heparin sulfate, thalidomide and spirulina platensis, photodynamic therapy with tin ethyl purpurin, and lately various methods involving anti-VEGF agents like bevacizumab[18].

During corneal NV, there is a disbalance between the angiogenic and antiangiogenic factors; which generally involves up-regulation of angiogenic factors and a downregulation of anti-angiogenic molecules. It plays a major angiogenic role in several ocular pathologies characterized by NV. It was recently shown that VEGF was up-regulated in inflamed and vascularized corneas in humans and animal models . Interestingly, requirement of VEGF in corneal NV was shown by the inhibition of NV after stromal implantation of an anti-VEGF blocking antibody in a rat model. VEGF promotes several steps of angiogenesis, including proteolytic activities, endothelial cell proliferation, migration, and capillary tube formation. Bevacizumab, a recombinant humanized monoclonal antibody developed against VEGF, binds to soluble VEGF, preventing receptor binding and inhibiting endothelial cell proliferation and vessel formation[19,20].

Topically administered bevacizumab was found to inhibit corneal NV after chemical injury in an experimental rat model[21,22]. In humans, a short-term follow-up study showed that local(topical or subconjunctival) bevacizumab reduced corneal NV in patients with significant corneal NV. As such the systemic administration of bevacizumab is reported to have a low incidence of adverse effects such as hypertension and thrombosis, however the small doses used in ocular conditions have so far not resulted in serious systemic effects. This study examined the effect of topical bevacizumab on corneal NV of various etiologies. In general, the treatment was found to reduce corneal NV[23,24].

In the present study, we therefore evaluated the efficacy of bevacizumab as an alternative treatment to reduce corneal NV after subconjunctival administration. Our study compares well with the report of Erdurmus et al in an article published in Graefe's Archive for clinical and experimental ophthalmology in 2007, where they had studied Subconjunctival bevacizumab for corneal neovascularization in two cases and the results showed that corneal NV was dramatically regressed a week after injection in the first case[25]. In the second case, minor vessels were regressed while the major one did not. In our series also the results showed regression of minor vessels in few cases while the major vessels seemed resistant to bevacizumab therapy. Also the study was well in confirmation with another study done by Bahar et al in 2008, where ten patients of corneal NV were included and they showed significant reduction of corneal NV. The improvement in terms of visual acuity was however only significant by Pearson chi square test and not by Wilcoxon signed Rank test (p=0.053).

Study with a longer duration of follow up (more than 6 months) can be taken in future to study the long term results. Also the improvement in visual acuity can be quantified in a larger study group. Further studies with different dosages and steroids combinations with the various VEGF inhibitors that compare not only the neovascularization itself but also the inflammatory response and side effects would contribute to the search for an ideal treatment.

Conclusions

This study concludes that subconjunctival bevacizumab (anti-VEGF agent) is a new and effective modality of reducing the corneal vascularization.

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