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Review Article

Expanding Therapeutic Horizons of Bevacizumab

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Abstract

Background: In the past few years there has been an increased interest in the repurposing of already approved pharmacotherapies for other uses. Bevacizumab is the most widely off-label used antiangiogenic in retinal ophthalmology, recently highlighting new targets in other ocular disorders.

Objective: The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that bevacizumab may be useful in the management of pterygium as an "off-label" drug.

Keywords: *Pterygium; Angiogenic Cascade; Bevacizumab*

Introduction

In the past few years there has been an increased interest in drug reprofiling due to sustained high failure rates and the rising costs involved in attempts to bring new drugs to the market [1].

Currently repurposing of approved drugs is widely accepted by the industry and encouraged by worldwide regulatory agencies. The general use of an approved medication for a new indication recognized by the medical community but not specifically indicated by a regulatory agency (FDA) is referred to as off-label use. Once the FDA approves a drug, ophthalmologists may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient. Specifically, the exploration of bevacizumab use in pterygium was a result due to a lack of treatment in effect. As researchers and practioners considered the properties of bevacizumab, it became reasonable to trial them in patients with pterygium.

The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that bevacizumab may be useful in the management of pterygium as an "off-label" drug.

Bevacizumab

Bevacizumab (Avastin, Roche), as a recombinant humanized monoclonal antibody, which neutralizes all isoforms of human VEGF and inhibits VEGF-induced proliferation of endothelial cells [2] is FDA-approved for the treatment of colorectal cancer. In the ophthalmology it has been widely used off-label since 2004 to treat several retinal diseases related to angiogenesis, such as neovascular macular degeneration, proliferative diabetic retinopathy, diabetic macular edema , retinal vein occlusion by intraocular injections, taken into account it's low cost. These findings are beyond the scope of this review.

Predictably rational current use of Bevacizumab in Pterygium

Pterygium is a common ocular surface disease triggered by ultraviolet light exposure, climate, inflammation and related to genetics [3-7], which manifests by vascularized conjunctival fibrous tissue invasion into the cornea with Bowman's layer involvement due to migration of abnormal limbal basal epithelial stem cells into owman's layer ended by it's resorbtion [8-11].

The only currently existed treatment for pterygium is a surgery, but frequent postsurgical recurrences [6-11] indicate a need for new avenues of successful intervention.

Currently available research findings underscore a role of VEGF in the pathogenesis of pterygium [12-14]. Human eyes with pterygium showed evidence of upregulated expression of VEGF in the epithelium of pterygium [14]. As pterygium is associated with increased levels of VEGF, anti-VEGF therapy was proposed to be a promising strategy for free of recurrences pterygium surgery due to blocked the angiogenic cascade with further fibrovascular tissue formation. Aforementioned indicates a clinical use of bevacizumab intended to decrease reccurrence rate in patients with pterygium.

Bevacizumab in eyedrops

The first use of topical bevacizumab (25 mg/ml) was documented by Wu., *et al*. [15] in 53-year-old woman with impending recurrent pterygium after failed surgery with mitomycin C. The patient was on bevacizumab drops 4 times daily for period of 3 weeks. This case report highlights the success of an eye drop administration route.

Considering the need for agents heightened success rate of pterygium surgery Fallah., *et al.* [16] conducted a study of 54 patients with impending recurrent pterygium and stated the short term efficacy of bevacizumab. Despite this statement it is not feasible to evaluate a real topical bevacizumab potential taken into account it's simultaneous use with mitomycin C.

The latest prospective randomized controlled study [17], based on results of 20 patients with bilateral primary pterygium , who underwent pterygium surgery with bare sclera approach and intraoperative mitomycin C, have focused on the combined use of intraoperative mitomycin C and Bevacizumab 1% solution as an eye drops 4 times a day for 4 weeks postoperatively comparing to mitomycin C alone.

It is recognized that there is a drive towards regression of corneal neovascularization. At the same time , evidence suggests that recurrence rate was not statistically significantly different in group additionally treated by bevacizumab.

Ozgurhan., *et al*. [18] evaluated efficacy of topical bevacizumab (four times a day for a month) in prospective interventional study of 44 patients with pterygium, who underwent surgery with conjunctival autograft (22 patients in case and 22 respectively in control group) with 6 months follow up and concluded that the good tolerated drug successfully retards corneal neovascularization, but failed to show evidence-based effect on pterygium reccurrence.

Similar findings were evidenced by Karalezli and coauthors [19] in the first prospective, randomized clinical trial with long-term follow-up (24 – 48 mo) based on results of 42 eyes operated with conjunctival autograft and treated by topical bevacizumab (5 mg/mL) for a month.

In summary, bevacizumab seems to have no beneficial effect on lowering the recurrence of primary pterygium when used topically after surgical excision.

Another randomized controlled trial measuring the efficacy of topical 0.05% Bevacizumab to inhibit the growth of recurrent pterygium were conducted by Kasetsuwan., *et al* [20]. The researchers randomized 22 patients into group receiving bevacizumab drops 4 times daily for 3 months -12 eyes and 10 eyes into placebo group , and monitored them once monthly with well-documented photoregistration by slit-lamp and masked analysis. At the end of follow-up period recurrences were documented in 4 (33.33%) treated patients and 9 (90.00%) placebo-receivers, evidencing significant difference and underscoring slow down trend in the bevacizumab treated arm. However, implications are limited due to small sample size.

In the latest comparative study of 90 patients [21] evaluating the efficacy of different concentrations of topical bevacizumab - 0.05% and 0.1% vs. placebo on the recurrence rate of pterygium with a very short-term-1 week follow-up study the authors concluded that 0.1% of topical bevacizumab instilled four times a day for one week was more efficacious than 0.05% solution in preventing pterygium recurrence.

Hwang and Choi [22] designed and conducted another study comparing selective retarding effect of topical mitomycin C, cyclosporine, and bevacizumab after excision of pterygium in 29, 34 and 36 patients respectively treated four times daily for three months by each drug

to control group (33 patients) also treated four times a day for three months with artificial tears evaluated at 6 months follow-up. In this study was used fortified bevacizumab -2.5%, but despite high concentration this agent failed to show ability to lower recurrence rates in contrast to mitomycin C and cyclosporine.

Scientific understanding of pterygium continues to develop, and recent changes have been made to how matrix metalloproteinase (MMP) expression/activity impacts on pterygium fibroblast migration [23], which underscores the importance of combined use of cyclosporine A and bevacizumab. In the latest in vitro study [23] examining pterygium and normal conjunctival specimens it has been demonstrated that initial pretreatment with cyclosporine A followed by bevacizumab administration results in significant block of cell migration and the expression of MMP-3 or MMP-13. Cyclosporine A enhances the inhibitory effects of bevacizumab on pterygium fibroblast migration, as supposed by researchers due to inhibiting expression of both subtypes of MMP. Thus, there is a new avenue of intervention being explored.

Summarizing, the advantage of Bevacizumab eye drop administration route is that it is convenient, noninvasive and avoids the untoward effects from a systemic load, but currently available findings obviate the need for further research allowing optimal patient management.

Bevacizumab in Subconjunctival injections

The first use of bevacizumab as a single subconjunctival injection in two cases of inflamed or residual pterygium was documented by Mansour [24]. This case report highlights successful regression of conjunctival microvessels.

According to the preliminary results of randomized controlled trial of intralesional bevacizumab injection on primary pterygium as an initial treatment approach [25], bevacizumab is able to manage inflammation and the following accompanying symptoms: irritation, photophobia, epiphora, redness, discharge, and blurred vision during 6 months follow up without serious ocular or systemic side effects.

The results from the most recent case series study conducted by Blerta and Sylaj-Lokaj [26] suggest that subconjuctival Bevacizumab injections as a non-surgical approach has not demonstrated significant changes in recurrence of pterygium.

Lekhanont., *et al*. [27] evaluated the efficacy of different dosages of subconjunctival bevacizumab in randomized controlled study of patients with impending recurrent pterygium . It has been shown that bevacizumab causes only temporary decrease in the conjunctival vascularization without any therapeutic impact including reccurence.

In case-control study conducted by Suh and Choi [28] on 54 patients after pterygium surgery in case group treated by subconjunctival bevacizumab injection evidence suggests an absence of slow down recurrence, despite blocked proliferation of fibrovascular tissues.

The results from meta-analysis conducted by Hu., *et al.* [29] directed to assess the efficacy and safety of topical and subconjunctival bevacizumab in the treatment of pterygium were based on randomized trials inclusive to July 2013, demonstrated safety and well tolerability of drug, but despite this fact suggest that bevacizumab use has not statistically significant impact.. At the same time the authors concluded that currently available findings obviate a need for new large-scale trial with a suitable dosage and a long-term follow-up to definitely clear the question.

Stival., *et al*. [30] in prospective case series of 36 patients with primary and recurrent pterygium treated by subconjunctival injection of 2.5 mg/0.1 mL bevacizumab with 2 months follow up period demonstrated pterygium manageability and good safety profile of intervention.

If bevacizumab is compared to 5-fluorouracil injection in pterygium surgery with autograft [31] in randomized controlled prospective study of 70 patients , it has been shown that despite the equal efficacy for both drugs to diminish reccurrency rate, bevacizumab is a preferred economic option from the point of it's low cost.

In contrast to the above mentioned studies, Singh., *et al*. [32] have reported only deterioration of neovascularization without impact on recurrence rate after bevacizumab subconjunctival injection in dose 1.25 mg/0.05 ml only 1 week before surgical exsicion.

But commenting on Singh study Shivalli and Kaur [33] stated that "The power (1-β) of this study is very low (0.51) with a sample size of 60 (30 in each group), even expecting a 20% absolute reduction in pterygium recurrence with subconjunctival bevacizumab when compared to 30% in control group. This may compromise the external validity of the findings".

The effects of anti-VEGF agents are often transient owing to the short half-life of the drug, and treatment schedule often requires multiple injections. Recently, there have been several studies conducted to evaluate the effect of multiple subconjunctival bevacizumab injections in patients with pterygium recurrence [34-37].

Nava-Castañeda., *et al.* [34] in randomized trial based on findings of 49 patients with primary pterygium, who underwent surgery with autograft evaluated and compared efficacy of single subconjunctival bevacizumab injection (2 .5 mg/0.1 mL) immediately after surgery in the first group to a double injection of the same dosage, one immediately after surgery and the second 15 days after surgery in the second group, to control group without injection with one year follow up period. Researchers demonstrated a single injection capability to prevent pterygium recurrences comparing to control group.

The findings of Bayar., *et al*. [35] underscores the potential of multiple injections of bevacizumab in preventing postsurgical recurrences especially in the first year after surgery.

A recent nonrandomized single center trial [36] Nava-Castañeda 2015) involving 38 patients with an early corneal pterygium recurrence, who received 3 subconjunctival bevacizumab (2.5 mg/0.1 mL) injections (initially, 2 and 4 weeks later) indicated that triple injections approach can retard the corneal opacification and neovascularization processes.

In randomized study by Razeghinejad and Banifatemi [37] subconjunctival bevacizumab was injected twice –initially (5 mg/0.2) on the day of surgery and 2.5 mg/0.1 mL on the fourth day after surgery in 22 patients with primary pterygium. It was found that while fibrovascular tissue crossing the limbus regressed twofold comparing to control group , bevacizumab efficacy does not reach statistical significance.

The literature review conducted by Mak., *et al*. [38] revealed that antiVEGF as a monotherapy for pterygium does not cause regression, despite manageable symptoms. The use of anti-VEGF as an adjuvant therapy to surgery, especially when using a higher dose and a more frequent dosing regimen is evidenced. However, available findings does not conclusively support the use of anti-VEGF in pterygium surgery.

In summary, the general consensus is that bevacizumab has a good safety and tolerability profile, but currently available findings on it's efficacy in preventing recurrences after pterygium surgery are controversial. It remains unclear whether subconjunctival injection is more effective than topical administration. A critical analysis reveals inadequate therapeutic threshold of bevacizumab with both routes of treatment. This would require the ophthalmologists to undertake an innovative approach to drug delivery, possibly by using bevacizumab-saturated bio-degradable punctum plug.

Conclusion

Management of pterygium poses challenge taken into account a high recurrence rate. Scientific understanding of pterygium continues to develop, and recent changes have been made to how VEGF is involved in the process of fibrovascular tissue formation, which underscores the importance of antiVEGF agents incorporation, specifically bevacizumab as a most affordable, in the treatment protocol. Bevacizumab offers a potential to slow down recurrences of pterygium after it's surgical excision. However, the need still exists to further assess the long-term effects, the best administration route, and treatment algorithm should be evidenced to make it a more viable option.

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