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Is Bevacizumab Effective in Inhibiting the Growth of Recurrent Pterygium?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not Bevacizumab is an effective treatment in inhibiting the growth of recurrent pterygium.

Study Design: Review of three published, English language randomized controlled trials published in 2010, 2012, and 2013.

Data sources: Three randomized controlled trials measuring the efficacy of Bevacizumab to inhibit the growth of recurrent pterygium were found using PubMed and OVID databases.

Outcome(s) Measured: The severity and progression of pterygium recurrence as well as corneal neovascularization were the main outcomes measured. Conjunctival injection, thickness, and size of the fibrovascular tissue were examined in subjects using ophthalmic evaluation including visual acuity testing, applanation tonometry, lit-lamp biomicroscopic examination, slit-lamp photography, indirect ophthalmoscopy, and corneal photographs.

Results: In the study by Fallah, all groups failed, meaning fibrovascular tissue stretched onto the cornea. However, the mean duration for invasion of cornea in study group patients was significantly longer than for control group patients. The study by Lekhanont showed that Bevacizumab significantly transiently decreased the conjunctival injection. However, true recurrence was found in 62 of 80 patients with no statistically significant difference among the groups. In the study by Ozgurhan, pterygium recurrence was not noted in any patients in the study group, but was noted in 2 of 22 eyes in the control group. Moreover, corneal neovascularization was noted in 5 of 22 eyes in the control group but in none of the patients of the study group.

Conclusion: The results of two of the randomized trials showed that Bevacizumab delays the recurrence of impending recurrent pterygium, but does not completely inhibit it. One of the randomized trials showed that Bevacizumab was an effective therapy for reducing recurrent pterygium and corneal neovascularization, but results were not statistically significant. Overall consistency was not provided and the data was inconclusive. All trials were limited due to small sample size and lack of follow-up studies.

Key Words: Recurrent pterygium; Bevacizumab; Avastin; VEGF

INTRODUCTION

Pterygium is a proliferative conjunctival lesion that consists of fibrovascular tissue and extends onto the cornea. It can cause significant astigmatism and severe visual impairment.⁶ Recurrent pterygium, which is not uncommon after pterygium excision surgery, can be more symptomatic and problematic to eliminate than primary pterygium.⁶ This systematic review evaluates three randomized controlled trials comparing the efficacy of Bevacizumab for inhibiting the growth of recurrent pterygium.

In 2013, the prevalence of pterygium worldwide was estimated to be 10.2%.⁹ Prevalence varies depending on the population studied, and it is more common in tropical regions.⁶ Within the U.S., prevalence rates vary from less than 2% to between 5% and 15% depending on locations.¹² Increased age and sun exposure are risk factor for the development of this lesion.⁶

Pterygium is usually managed by ophthalmologists, but it may be initially identified and treated by general practitioners. There are relatively few Physician Assistants (PAs) working in ophthalmology today.⁷ However, the U.S. is currently facing a projected shortage of ophthalmologists, and one solution may be for ophthalmologists to work with more PAs.⁷ The exact healthcare cost of pterygium has not been specified; however, the cost of vision-related diseases in 2013 was estimated to be \$139 billion.¹ The average cost of pterygium excision surgery with grafting is estimated to be \$3,000.³ An exact number of healthcare visits for pterygium was not specified; however, the number of ambulatory care visits for disorders of the eye and adnexa, excluding glaucoma, cataract, disorders of refraction and accommodation, conjunctivitis, and disorders of eyelids, was 11,899 in 2009.²

The natural history, etiology, and pathogenesis of pterygium are poorly understood. It is unclear how pterygium converts from active, which refers to growing over months to years, to

inactive, which refers to static without increase in size.⁶ It is believed that angiogenesis plays a key role in the formation of fibrovascular tissue in recurrent pterygium.¹⁰ The most common symptoms of pterygium range from none to redness, irritation, pruritus, discomfort, swelling, and blurring of vision.⁶ Pterygium may induce astigmatism, and it can cause adverse effects on vision if proliferation reaches the visual axis.^{6,12} Patients with a small pterygium are treated symptomatically with ocular lubricants; larger lesions that impair visual acuity or eye movement are treated by surgical excision of the lesion.⁶ Recurrence rates after pterygium surgical excisions are high, and the recurrent lesions may be more inflamed or grow larger than the initial lesions.⁶

Intraoperative and postoperative adjunctive treatment modalities to prevent recurrence of pterygium currently used include mitomycin C, 5-fluorouracil, corticosteroids, and beta irradiation.⁴ Currently used adjunctive measures decrease recurrence rates substantially, but reported rates vary widely, and none have been proven to be completely safe and effective.⁴ Pterygium recurrences and repeated excisions can lead to disruption of the ocular surface and subsequent complications.⁶ As mentioned earlier, angiogenesis has been noted to be a factor in pterygium formation and progression.¹⁰ Vascular endothelial growth factor (VEGF) is one of the most important factors in angiogenesis; therefore, blocking this factor may inhibit angiogenesis.¹⁰ Bevacizumab is an anti-VEGF agent and is thought to have potential value in the inhibition of growth of recurrent pterygium by inhibiting angiogenesis.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Bevacizumab is an effective treatment in inhibiting the growth of recurrent pterygium.

METHODS

This review consists of three prospective, randomized controlled trials that met certain criteria. The population studied included subjects over 18 years old who developed recurrent pterygium after pterygium surgical excision. Two of the studies reviewed compared Bevacizumab to topical corticosteroids (Lekhanont⁸, Fallah⁴) and one of the studies compared Bevacizumab to artificial tears (Ozgurhan¹⁰). More specifically, the interventions compared in the study by Ozgurhan were the use of topical Bevacizumab (5mg/mL) QID x 2mo vs. artificial tears QID x 2mo; this was a double blinded study, and the administration of both interventions took place one month after subjects had recurrent pterygium excision surgery. Lekhanont compared using a single intralesional subconjunctival injection of Bevacizumab at 3 different doses: 1.25 mg/0.05mL; 2.5mg/0.1mL; 3.75mg/0.15mL vs. topical 0.1% fluorometholone eye drops QID x 4wks. Finally, Fallah compared the use of 1 eye drop of Bevacizumab 5mg/mL BID with betamethasone QID for 1 week vs. betamethasone QID for 1 week only.

The outcomes measured in all three studies were all based on patient oriented evidence that matters (POEMS). The progression and severity of the pterygium in subjects' eyes after having had pterygium excision surgery was the main outcome measured. The severity of impending recurrent pterygia was measured by looking at conjunctival injection thickness, size and thickness of fibrovascular tissue, and scleral vessels as well as corneal neovascularization. Side effects and complications after applying treatment were also measured to assess the safety and tolerability of Bevacizumab for the treatment of pterygium.

Key words used to research for this topic included recurrent pterygium, Bevacizumab, Avastin, and VEGF. All three articles were published in English, and published in peer-reviewed journals. The author researched the articles using PubMed, OVID, and COCHRANE databases.

Articles were selected based on their relevance to the author's clinical question and whether they included POEMS. Inclusion criteria during the author's research included randomized controlled trial prospective studies published after 1999. The three studies selected were published between 2010 and 2013. Exclusion criteria included studies that included subjects under 18 years old with a past medical history of any ocular surface disease or any other ocular surgery besides the ones being currently studied. The statistics reported and used were numbers needed to treat (NNT), relative benefit increase (RBI), absolute benefit increase (ABI), relative risk increase (RRI), absolute risk increase (ARI), numbers needed to harm (NNH), and p-values.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ozgurhan, 2013	RCT	44	20-77	Pts. 18 years and older who had recurrent pterygium as well as the ability to provide written informed consent and to comply with assessments for the full duration of the study.	History of a major systemic condition or any ocular surface disease besides pterygium, uveitis, retinal vascular diseases, and previous conjunctival or scleral surgery	0	Use of topical bevacizumab (5mg/mL) QID x 2mo VS. artificial tear QID x 2mo

Lekhanont, 2012	RCT	80	31-67	Impending recurrent pterygium developed within 6 months after pterygium surgery Failure of conventional topical anti-inflammatory therapy for impending recurrent pterygium. 18y or older and good compliance with study regimen.	Hx of any adjunctive treatment, such as mitomycin C. Other ocular surface pathologies or coexisting ocular diseases. Hx of allergy to the medications used in the study. Other ocular surgeries within the previous 6mo.	0	Single intralesional subconjunctival injection of Bevacizumab at 3 different doses: 1.25 mg/0.05mL; 2.5mg/0.1mL; 3.75mg/0.15mL VS Topical 0.1% fluorometholone eye drops QID x 4wks
Fallah, 2010	RCT	54	>18	Pts. Who had undergone pterygium excision and developed impending recurrent pterygium.	Anterior surface complications or any other ocular surgery. Pts. With platelet disorders or HTN.	0	1 Eye drop of bevacizumab 5mg/mL BID with betamethasone QID for 1 week VS Betamethasone QID for 1 week only

OUTCOMES MEASURED

The main outcome measured was an increase in the size of fibrovascular tissue or true pterygium recurrence, which was defined by conjunctival fibrovascular tissue extending onto the cornea. The severity of impending recurrent pterygium was assessed depending on the scoring of conjunctival injection, thickness, and size of the fibrovascular tissue. Neovascularization was assessed by the presence of new vessels extending onto the cornea without conjunctival fibrous

tissue. Subjects underwent ophthalmic evaluation including visual acuity testing, applanation tonometry, lit-lamp biomicroscopic examination, slit-lamp photography, indirect ophthalmoscopy, and corneal photographs. Visual analog scales were used to evaluate symptoms and signs such as ocular irritation. These were recorded in a double-blinded fashion. Adverse reactions and complications were compared between study groups.

RESULTS

In the study by Ozgurhan, 44 eyes of 44 subjects at the Beyoglu Eye Research and Training Hospital, located in Istanbul, Turkey, were studied for a total of 6 months. Subjects were seen before having recurrent pterygium excision surgery, and were thereafter seen at 1 day, 1 week, 1 month, 2 months, 3 months, and 6 months after surgery. Treatments were applied at the 1month follow up visit. No instances of pterygium recurrence were noted in the study group, whereas recurrence in 1 eye was noted 1month after treatment in the 2 month follow up visit, and one additional recurrence was noted 2 months after treatment in the 3 month follow up visit. A total recurrence in 2 eyes of the control group was present at the 6 month follow up visit. However, this was not considered to be statistically significant ($p=0.244$). The patients in the control group who failed received topical Bevacizumab, which resulted in the inhibition of the advancement of their pterygium.

Corneal neovascularization was not seen in the patients in the study group. However, it was seen in 4 eyes of the control group in the 2 month follow up visit ($p=0.053$), and in 1 eye in the 3month follow up visit ($p=0.024$). A total of 5 eyes in the control group developed corneal neovascularization by the 6 month follow up visit ($p=0.024$); a statistical significant was noted between treatment and control groups based on the p value. Topical Bevacizumab was also given

to these patients in the control group who failed, which prevented corneal neovascularization from advancing and even thinned some of the vessels.

None of the subjects withdrew from the experiment, and all of the subjects' results were provided. SPSS version 16 was used for statistical analysis. The calculations for efficacy and safety can be seen in Table 2. The NNT was calculated to be -11 and is interpreted as followed: for every 11 patients treated with Bevacizumab, one fewer would experience inhibition in pterygium recurrence compared to control. There were no systemic or ocular side effects experienced by subjects who were administered the topical Bevacizumab. To measure safety of these medications, NNH was calculated and the result was -4. This would be interpreted as followed: For every 4 patients treated with Bevacizumab, one less would experience adverse effects.

Table 2: Bevacizumab and Pterygium Ozgurhan Study¹⁰

CER	EER	RBI	ABI	NNT	p-value
0.09	0	-1	-0.09	-11	0.244

CER	EER	RRI	ARI	NNH	p-value
22.7%	0%	-1	-22.7%	-4	0.024

In the study by Lekhanont, 80 eyes of 80 subjects were recruited in the eye clinic at the Ramathibodi Hospital, Bangkok, Thailand. Subjects chosen had developed recurrent pterygium in a mean time of 2.5 months after having pterygium excision surgery. Each treatment was given to subjects and then followed from 3-18 months. 3 days after application of the respective treatments, conjunctival injection significantly decreased in all treatment groups. 1 week after treatment, only the groups who received 2.5mg and 3.75mg of Bevacizumab continued to show a

significant reduction in conjunctival vascularization. Decrease in conjunctival injection was observed until 2 weeks for the group who received 2.5mg of Bevacizumab, and until 3 weeks for the group that received the highest dose of Bevacizumab, 3.75mg. At later points, conjunctival hyperemia increased back to its pre-injection states at later time points. Patients in the control group who received the topical corticosteroid only showed no regression of vessels at any point during the duration of the study.⁸

No significant difference in the mean severity score improvement among the treatment groups was observed, and no change in thickness and size of the pterygia was noted at any Bevacizumab doses during the study. At the 3 month follow up, true pterygium recurrence was found in 62 subjects. No statistically significant difference in the recurrence rate was noted among the groups ($p=0.82$). Recurrent pterygia showed to have a greater fibrovascular proliferative response than the original pterygia, and rebound hyperemia and inflammation were seen in the majority of the subjects. Side effects from the Bevacizumab treatment included pain after injection and subconjunctival hemorrhage; these were noted in 3 subjects.

A single subconjunctival Bevacizumab injection was effective in temporarily reducing conjunctival vascularization in impending recurrent pterygium; it had no effect on the size and thickness of the lesions. It was shown that Bevacizumab is unlikely to reduce the recurrence rate for impending recurrent pterygium. Statistical analysis was performed using SPSS version 14; Paired t test and Wilcoxon signed rank test were also used to determine the significance of changes after treatment. Results for calculations of efficacy and safety can be seen in Table 3. The NNT for this study is 4 and is interpreted as followed: For every 4 patients treated with Bevacizumab, one additional patient will have inhibition of the pterygium.

Table 3: Bevacizumab and Pterygium: Lekhanont Study⁸

CER	EER	RBI	ABI	NNT	p-value
80%	75%	-0.0625	0.25	4	0.82

In the study by Fallah, 54 eyes of 54 patients who developed recurrent pterygium after having pterygium excision surgery were randomly divided into treatment and control groups and followed for 3-6 months. Subjects were recruited from the Tehran University Eye Research Center. The mean ages of the treatment group and control group were 49.96 and 51.61 respectively; the age ranges of the subjects were not provided. It was noted whether the patients started the treatment 30 days prior to or 30 days following pterygium surgery. Means of progression of fibrovascular tissue were measured in the first week, first month, and three months of follow up after treatment was given to each of the groups.

The data in the study was continuous, and was unable to be converted into dichotomous data. The duration of progression of fibrovascular tissue to invasion of the cornea was calculated, and results were analyzed using the software SPSS version 13. All patients in both groups failed, meaning that fibrovascular tissue spread onto the cornea. However, Table 4 shows there was a statistical significance difference ($p < 0.01$) in time in which this happened between the groups. The duration for invasion of cornea was longer in the treatment group, and the mean progression of fibrovascular tissue was less than in the control group. Table 5 shows there was also a statistical significance in the time needed for invasion of the cornea with fibrovascular tissue in treatment patients compared to control patients when the drugs were started less than 30 days and more than 30 days following surgery.

Table 4: Progression after starting treatment⁴

	Treatment group	Control group	P value

One week	1.916± 0.375	2.740± 0.517	<0.01
One month	15.998± 1.22	27.230± 4.700	<0.01
Three months	37.671± 13.1	59.247± 9.472	<0.01
Time for corneal invasion (days)	90.538±51.569	44.892±18.905	<0.001

Table 5: Duration for corneal invasion following initiation of treatment after surgery⁴

	<30 days	>30 days	P value
Treatment group	119.6± 52.6	61.4± 30.5	0.002
Control group	54.0± 20.8	34.3± 8.4	0.004

DISCUSSION

This systematic review investigated three RCTs for the effectiveness of Bevacizumab in inhibiting the growth of recurrent pterygium. Each article selected subjects who had recurrent pterygium after having previous pterygium excision surgery. The blinding during the 3 RCTs was without error, and none of the subjects withdrew from the experiments.

Bevacizumab is a monoclonal antibody considered to be an anti-angiogenesis agent due to its ability to inhibit VEGF.⁵ It is currently approved by the FDA to be used as a first line drug against metastatic colorectal cancer.⁵ Some of the most common systemic side effects include epistaxis, thromboembolic events, hypertension, rhinitis, and proteinuria.⁵ Intravitreal Bevacizumab has been used as an off label treatment of age related macular degeneration with good results.¹¹ Although no systemic side effects and no obvious safety outliers have been noted with intravitreal use, more studies need to be done to determine the safety of topical Bevacizumab.¹¹

All three studies used different dosages of Bevacizumab, and in one of the studies Bevacizumab was given along with a topical corticosteroid. There were several limitations

expressed by each study. The study by Lekhanont noted that the dose of Bevacizumab given might have been insufficient to have the desired effect.⁸ The treatment was given 2.5 months after the excision surgery, and it was noted that the treatment might have been more effective if given sooner after surgery, before regrowth of fibrovascular tissue already occurred.⁸ Small sample size and short follow up time were further limitations noted.⁸ The study by Fallah noted that the quantity and limited amount of time Bevacizumab was administered to subjects was the main possibility for the treatment's failure.⁴ Finally, the study by Ozgurhan noted that the small sample size and short follow up time were the main limitations in the study.¹⁰

CONCLUSIONS

Two of the studies showed that Bevacizumab is not an effective treatment in inhibiting the growth of recurrent pterygium; however, they showed that it delayed the recurrence of the disorder. The other study showed inhibition of growth in pterygium, however, the results were not statistically significant. Therefore, the evidence analyzed in this systematic review is inconclusive. Future study is warranted to evaluate topical Bevacizumab as a treatment to inhibit the growth of recurrent pterygium before routine use can be recommended and approved by the FDA.

Future studies evaluating the effectiveness of Bevacizumab should include larger study groups within the United States. There should also be a more consistent amount of time between the pterygium excision surgery and the start of treatment in the study groups. The results of the studies analyzed in this systematic review demonstrated significant potential of Bevacizumab to inhibit recurrent pterygium. Current ongoing studies are being done in England and in the U.S. to determine the effectiveness of Bevacizumab in the treatment of choroidal neovascularization which will help shed light on the safety of the drug when applied topically.¹¹

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