

# Overview of Bevacizumab (Avastin) Utility against Neovascularization in Corneal Keratoplasty

## Po-Yuan Chen<sup>1,2\*</sup>

<sup>1</sup>Department of Medicine, College of Medicine Chang Gung University, Taoyuan, Taiwan;<sup>2</sup>Department of Ophthalmology, Chang Gung Memorial Hospital, Linkou, Taiwan

## ABSTRACT

Neovascularization is a primary risk factor in keratoplasty. Multiple measures were implemented to prevent vascularized cornea, including bevacizumab (anti-VEGF) treatment. Bevacizumab inhibits angiogenesis and lymphangiogenesis, and induce vasoconstrictive effect. There are different modalities of administration of Bevacizumab, including topical pathway, which is administered is less invasively but were doubted of its efficacy due to its penetration rate of the corneal epithelium tight junctions of intact cornea. Intrastromal (corneal) injection is expected to increase the concentration and exposure time of the drug in the stromal layers, providing a more effective exposure than topical or subconjunctival application. Besides, early administration of anti-VEGF factor for early high-risk patients of possible NV showed better clinical result. Ophthalmologists should consider every aspect of the patient's clinical status before deciding whether and how bevacizumab is given in a corneal graft recipient. Keywords: Bevacizumab (Avastin); Anti-VEGF; Neovascularization; Keratoplasty

# INTRODUCTION

Neovascularization had been reported in different studies as a key risk factor for early graft rejection and further poor prognosis of corneal graft in different types of keratoplasty (including penetrating keratoplasty, DSAEK (Descemet Stripping Automated Endothelial Keratoplasty), or DALK (Deep Anterior Lamellar Keratoplasty) [1]. Vascularization though being an immune response, may disrupt the clarity of the cornea and lead to corneal scarring, edema, and lipid disposition causing reduction in visual acuity. Mechanism behind NV (Neovascularization) and poor prognosis had been widely studied; including losing of immunological privilege of anterior chamber-associated immune deviation. Lymphogenesis, although mostly invisible under slit lamp examination, may result in contact between the recipient's secondary lymphoid organs with the graft leading to accelerated sensitization against donor antigen and augmented access of immune effector cells to the graft [2].

Hence, multiple approaches had been implemented to prevent or treat vascularized cornea and reduce the risk of graft rejection. These measures could be classified into three dimensions. First of all, angio-static approaches, including improvements in surgical methods and techniques, immunological or racial matching; for instance HLA antigen, and various types of immune modulating drugs, such as Cyclosporine A, Mitomycin C, Sirolimus. Besides, angio-regressive approaches, including anti-VEGF and angiopoietin-2, are dedicated for regression of the newly formed pathological vessels [3]. While, angio-occlusive approaches include modalities such as fine-needle thermal cauterization and argon laser act by occluding the wellestablished formed vessels.

In all of the forward mentioned methods to maintain the angiogenic privilege of cornea, none more important than the endogenous inhibition of VEGF (Vascular Endothelial Growth Factor). VEGF promotes many steps in angiogenesis, including proteolytic activities, cellular proliferation, endothelial cell proliferation and migration, and capillary tube formation. Hence, when NV occurred, direct administration of anti-VEGF become a possible solution to inhibit inflammation-mediated, pathologic corneal NV [4]. Bevacizumab is the most well-practiced and effective anti-VEGF in ophthalmology field,

Corresponding Author: Po-Yuan Chen, Department of Medicine, College of Medicine Chang Gung University, Taoyuan, Taiwan; E-mail: willy8421384213@yahoo.com.tw

Received: June 23, 2021; Accepted: July 7, 2021; Published: July 14, 2021

**Copyright:** © 2021 Chen PY. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Citation: Chen PY (2021) Overview of Bevacizumab (Avastin) Utility against Neovascularization in Corneal Keratoplasty. J Clin Exp Ophthalmol. S8:001.

comparing to ranibizumab or other similar antiangiogenic substances. bevacizumab is a full-length, recombinant monoclonal antibody that binds all VEGF isoforms which blocks vascular permeability and angiogenesis by inhibiting the VEGF-receptor interaction.

It is currently widely "off label" used in corneal transplantation and other NV related eye disease to improve overall outcomes, with promising results [5]. Besides, neutralization of corneal VEGF may also tip the local vasodilatory such as Endothelins and vasoconstrictive factors towards vasoconstrictive factors reducing the perfusion of established and not-regressing vessels. Further downregulation of VEGF by siRNA retards corneal NV and significant decrease VEGF mRNA level, suggesting more complex roles for bevacizumab in anti-NV therapy [6]. Moreover, in some scientific reports, lymphangiogenesis although mostly invisible under slit lamp examination, was also VEGT-A dependent, and if inhibited may further halt leukocytes proliferation through blocking the contact between the recipient's lymph vessel and the graft, and improve graft survival.

In recent practice, anti-VEGF therapy was performed in different route and both pre and postoperative in high-risk corneal transplantation with NV and improve prognosis for graft survival. It replaced part of the role of topical steroid as an effective treatment against vascularization of the graft in clinical routine [7]. Because of serious side effects during long-term usage of topical steroid. It prevented common complications include secondary glaucoma and cataract formation and risk of infections, especially HSV recurrence with further longstanding, high-dose therapy of steroid. Herein, we present a brief review of the recent update of bevacizumab implementation in the field of corneal transplantation [8].

# DISCUSSION

### Complications of bevacizumab

Complication rate is always the first issue to consider in off-label use. There were several case series describing bevacizumab complications in different administering routes [9]. A case of limbal ischemia, recipient bed melt, and wound dehiscence with problem of re-epithelization corresponding to bevacizumab injection site was reported. Observed developing of descemetocele and epitheliopathies in six of ten eyes under topical bevacizumab treatment. These complication may be attributable to the antifibrotic effects of anti-VEGF disrupting the growth factor and mediator signal transduction cascade in fibroblast migration and proliferation, affecting corneal nerve degeneration, interfere with macrophage recruitment and causing reduction of caliber of surrounding blood vessels; these together may contribute to a negative effect of the corneal wound healing process [10]. The negative effects of topical bevacizumab seems to be dose dependent using 12.5 mg/ml of topical bevacizumab whereas, using lower dose with 5mg/ml showed little adverse effect in the whole course of treatment. However, there is little evidence of negative effect of bevacizumab regarding epithelial healing or surrounding tissue in most case reports and small case series.

Limitation of anti-VEGF treatment and alternative treatment modalities.

The effect of anti-VEGF substances on long-existing established vessels is not as strong as on growing, active vessels. Mature vessels covered with pericytes become angiogenic factor independent. In contrast, new vessels in latent pre-vascular phase and active NV phase (around <12 weeks of formation) lack pericyte coverage, and have fewer layers of basement membranes and tight junctions [11]. Hence, removing the bulky abnormal corneal tissue in keratoplasty, instead of administering anti-VEGF seems to reduce the stimulus for vessel regrowth evidently and showed promising result. Alternatively, laserinduced photocoagulation or fine-needle diathermy combined with bevacizumab administration usually lead to well-tolerated and better treatment result of mature vessels. Solitary treatment of mature NV with laser-induced photocoagulation or fineneedle diathermy may cause influx of proangiogenic inflammatory cells and further angiogenesis noted in experimental studies.

#### Different administration routes of Bevacizumab

Topical bevacizumab administration is less invasive but were doubted of its efficacy due to its penetration rate of the corneal epithelium tight junctions of intact cornea and the actual compliance of patients in several studies. However, ocular surface disease may cause inflammation, which weakened the barrier of large molecules and increase penetration rate [12]. Hence, topical bevacizumab administration did show some benefit result when treating NV in different clinical settings. However, the effect may be slow onset, with strongest regression of corneal vessel thickness appeared to happen within the first 3 months of treatment. Comparing to topical bevacizumab, subconjunctival or intravitreal less common due to its higher systemic dose and complication bevacizumab approach perform superiorly in specific groups of transplant patients [13]. These approaches were assumed that some of the bevacizumab would diffuse slowly into the anterior segment, this procedure may result in a low-level, longer standing effect of VEGF inhibition, and better compliance rate. In the in vivo studies of using mice cornea as model organism, both topical and subconjunctival bevacizumab treatment reduced neovascular area and vessel caliber; however, the regression of corneal NV was faster and more evident, which also promotes graft survival in the high-risk setting when treated subconjunctivally. In the randomized casecontrolled studies performed by Nasir Bhatti and his colleagues had similar results, with reduction of NV, and graft survival was both better in subconjunctival administration compared with topical administration [14].

Intrastromal (corneal) injection is a novel route of bevacizumab injection, which was expected to increase the concentration and exposure time of the drug in the stromal layers, providing a more effective exposure than topical or subconjunctival application. It avoided logistical difficulty of administering topical drug, and showed somewhat encouraging results of treating NV in some small case series. Besides, systemic antiVEGF exposure is also lower comparing to intravitreal or subconjunctival administration, lessen the severely and chance of potentially life-threatening systemic adverse events. Transitory corneal edema without progressing to corneal necrosis or chronic epithelial defect was reported. Other less popular approaches being implemented in case report or small case series included direct drug injection at the interface or perilimbal injection after DALK (Deep Anterior Lamellar Keratoplasty), and soaked corneal light shield to increase exposure time of the cornea to the medication [15].

#### Timing to apply bevacizumab treatment

In recent practice, bevacizumab is still mostly administered as part of the treatment plan of the latent pre-vascular NV observed in pre- or postoperative period. However, since the complication rate of administering local bevacizumab is minimal, especially at low dosage. Preconditioning adjuvant administering of bevacizumab in high-risk corneal transplantation to prevent graft rejection was supported in murine model, and was also further investigate in a few casecontrol studies. High-risk corneal transplantation, including highly vascularized leucoma, advanced pseudophakic bullous keratopathy, keratoconus, corneal combustion, infection ulcer, failed the corneal graft, and Stevens-Johnson Syndrome (SJS). In these groups, the risk of had been shown to correlate with the number of corneal quadrants NV. In the 27 patients (case group: 14 eyes and control group: 13 eyes) randomly designed prospective study which investigate whether adjuvant subconjunctival and intrastromal preconditioning bevacizumab injection help overall prognosis of corneal grafts in the patient group of high-risk keratoplasties. The effect of graft prognosis seems equivocal, probably due to the short follow up period (mean follow up 3.8 months); nevertheless, less ocular and corneal inflammation, related to less congestion, caliber reduction, and possible less exposure of graft antigen was noted during postoperative period [16]. In short, for high risk patients of possible NV, better clinical result could be achieved under therapeutic strategies aiming at regression of blood vessels using anti-VEGF factor (even through topical route) as early as possible. Preconditioning adjuvant therapy with subconjunctival and intrastromal bevacizumab injections could be considered to promote possible long-term corneal graft survival.

## CONCLUSION

Bevacizumab contained complex mechanisms in preventing occurrence of NV, which lead to better visual outcome and lesser acute rejection rate of grafts in keratoplasty. Multiple routes and timing of administration of bevacizumab had been investigated, and mostly showed some degree of effectiveness, with different pros and cons. Ophthalmologists should consider every aspect of the patient's clinical status before deciding whether and how bevacizumab is given in a corneal graft recipient. Future controlled prospective randomized trials are also necessary to learn more about the long-term safety and benefit, optimal dosage and efficacy of these approaches.

# CONFLICT OF INTEREST

The authors declare no conflict of interest.

## REFERENCES

- Hsiao FC, Chen PY, Meir YJJ, Tan HY, Hsiao CH, Lin HC, et al. Clinical outcomes of penetrating keratoplasty and descemet stripping automated endothelial keratoplasty in asian population with american corneas. Int J Environ Res Public Health. 2019;16(22):4547.
- Jarrin E, Ruiz-Casas D, Mendivil A. Efficacy of bevacizumab against interface neovascularization after deep anterior lamellar keratoplasty. Cornea. 2012;31(2):188-190.
- Vassileva PI, Hergeldzhieva TG. Avastin use in high risk corneal transplantation. Graefes Arch Clin Exp Ophthalmol. 2009;247(12): 1701-1706.
- Bock F, Onderka J, Dietrich T, Bachmann B, Kruse FE, Paschke M, et al. Bevacizumab as a potent inhibitor of inflammatory corneal angiogenesis and lymphangiogenesis. Invest Ophthalmol Vis Sci. 2007;48(6):2545-2552.
- Hsiao FC, Chen PY, Meir YJJ, Tan HY, Hsiao CH, Lin HC, et al. Clinical outcomes of penetrating keratoplasty and descemet stripping automated endothelial keratoplasty in asian population with american corneas. Int J Environ Res Public Health. 2019;16(22):4547.
- 6. Jarrin E, Ruiz-Casas D, Mendivil A. Efficacy of bevacizumab against interface neovascularization after deep anterior lamellar keratoplasty. Cornea. 2012;31(2):188-190.
- Vassileva PI, Hergeldzhieva TG. Avastin use in high risk corneal transplantation. Graefes Arch Clin Exp Ophthalmol. 2009;247(12): 1701-1706.
- Bock F, Onderka J, Dietrich T, Bachmann B, Kruse FE, Paschke M, et al. Bevacizumab as a potent inhibitor of inflammatory corneal angiogenesis and lymphangiogenesis. Invest Ophthalmol Vis Sci. 2007;48(6):2545-2552.
- Seitz B, Langenbucher A, Kuchle M, Naumann GOH. Impact of graft diameter on corneal power and the regularity of postkeratoplasty astigmatism before and after suture removal. Ophthalmology. 2003;110(11):2162-2167.
- Razeghinejad MR, Hosseini H, Ahmadi F, Rahat F, Eghbal H. Preliminary results of subconjunctival bevacizumab in primary pterygium excision. Ophthalmic Res. 2010;43(3):134-138.
- Birnbaum F, Bohringer D, Sokolovska Y, Sundmacher R, Reinhard T. Immunosuppression with cyclosporine A and mycophenolate mofetil after penetrating high-risk keratoplasty: A retrospective study. Transplantation. 2005;79(8):964-968.
- 12. Kruse FE, Volcker HE. Stem cells, wound healing, growth factors, and angiogenesis in the cornea. Curr Opin Ophthalmol. 1997;8(4):46-54.
- 13. Hos D, Le VNH, Hellmich M, Siebelmann S, Roters S, Bachmann BO, et al. Risk of corneal graft rejection after high-risk keratoplasty following fine-needle vessel coagulation of corneal neovascularization combined with bevacizumab: A pilot study. Transplant Direct. 2019;5(5):e452.
- 14. Singh N, Higgins E, Amin S, Jani P, Richter E, Patel A, et al. Unique homologous siRNA blocks hypoxia-induced VEGF upregulation in human corneal cells and inhibits and regresses murine corneal neovascularization. Cornea. 2007;26(1):65-72.
- Agarwal S, Angayarkanni N, Iyer G, Srinivasan B, Natarajan R, Charola S, et al. Clinico-biochemical correlation of the effect of subconjunctival bevacizumab for corneal neovascularization. Cornea. 2014;33(10):1016-1021.
- Benayoun Y, Adenis JP, Casse G, Forte R, Robert PY. Effects of subconjunctival bevacizumab on corneal neovascularization: Results of a prospective study. Cornea. 2012;31(8):937-944.