ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 04 | April - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

REVIEW ARTICLE: CORNEAL VASCULARIZATION

Ophthalmology

Dr Rakesh Kumar M S Ophthalmology, Civil Hospital, Palampur. District-Kangra H.P. 176061.INDIA.

Dr Smriti Sharma* M S Ophthalmology, Civil Hospital, Palampur. District-Kangra H.P. 176061.INDIA. *Corresponding Author

ABSTRACT

Transparency and lack of blood vessels are unique attributes of the cornea. The latter is in many ways a prerequisite for the former. The cornea has evolved to keep blood vessels away and many factors contribute to this. The compactness of the corneal stromal architecture is considered to be an impediment to vessel invasion. When the cornea is stressed by such events, new blood vessels invade the corneal tissue to fulfill this role. A multitude of conditions induce new blood vessels to invade the cornea, resulting in 'corneal vascularisation' (neovascularization) Angiogenesis refers to new blood vessels that originate from pre-existing vascular structures. Corneal neovascularization which can lead to compromised visual acuity occurs in a wide variety of corneal pathologies. Corneal neovascularization occurs when the balance between angiogenic and antiangiogenic factors is tipped toward angiogenic molecules. Vascular endothelial growth factor (VEGF), one of the most important mediators of angiogenesis, is up regulated during neovascularization. Several therapeutic strategies are in clinical use for restoring corneal clarity in case of CNV. Depending on degree and anatomical position of CNV surgical techniques like cauterization, lamellar keratectomy or corneal lamellar or perforating keratoplasty can restore the patient's vision.

KEYWORDS

INTRODUCTION

A healthy cornea is a transparent, avascular tissue located anterior to the iris and the pupil. Maintaining transparency and avascularity is essential to preserve optimal vision as well as protect the eye against infections and structural damage. Corneal neovascularization (CNV) is the in-growth of new blood vessels from the pericorneal plexus into avascular corneal tissue as a result of oxygen deprivation.[1] This occurs due to a wide variety of ocular insults, including infection, inflammation, ischemia, degeneration, trauma, and loss of the limbal stem cell barrier. Corneal pathologies that can lead to neovascularization include lipid keratopathy, corneal ulcers and scars, herpes eye disease, infectious keratitis, chemical burns, graft rejections and hypoxic insults from contact lens wear.[2,3]

One study reported the estimated incidence rate of 1.4 million people per year, 12% of whom suffered subsequent loss of vision.[4] Established mature blood vessels do not require angiogenic growth factors, whereas immature blood vessels are dependent on them for proliferation, hence treatment is aimed at either removal of established vasculature or preventing neoangiogenesis [5]

Pathophysiology of Corneal Neovascularization

The in-growth of new blood vessels is mediated by the upregulation of angiogenic cytokines. The enzyme metalloproteinase degrades the cornea's basement membrane and extracellular matrix, while proteolytic enzymes allow vascular epithelial cells to enter the stromal layer of the cornea.

When ocular inflammation occurs, corneal epithelial and endothelial cells, macrophages and certain inflammatory cells produce angiogenic growth factors, namely vascular endothelial growth factor (VEGF) and fibroblast growth factors. VEGF paves the way for new blood vessel formation by upregulating matrix metalloproteinases production by endothelial cells in the limbal vascular plexus. [6] Angiogenic chemical mediators consist of vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGFs), and interleukin-1 (IL-1). [7,8]. The so-called VEGF family include VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor in mammals. [9] VEGF-A is the most significant member of the VEGF family and is secreted by a wide variety of heterogeneous cells, such as macrophages, T-cells, fibroblasts, pericytes, astrocytes, retinal pigment epithelial cells, and corneal cells (epithelium, keratocytes, and endothelium.[10] Macrophages, stimulated by inflammation or injury, can also secrete VEGF-C and VEGF-D in the corneal stroma. [11] VEGF-A propagates its effect by interacting with tyrosine kinase receptors; VEGFR-1 and VEGFR-2. VEGFR-1 is a transmembrane receptor tyrosine kinase, whereas VEGFR-2 is a major signalling receptor for VEGF that prompts the proliferation and migration of vascular endothelial cells. [12] Lymphangiogenesis can be stimulated by VEGF-C and VEGF-D through interaction with VEGFR-3. [13,14]

VEGF is not the only biological molecule playing the roles of hemangiogenesis and lymphangiogenesis. Other factors associated with corneal neovascularization are PDGFs that are involved in tissue remodelling, cell growth and division, and angiogenesis. It has been demonstrated that the interactions of ligands, such as PDGF-A and PDGF-B, with their corresponding receptors (PDGFR-a and PDGFR-b), are associated with corneal neovascularization. [15,16] bFGF promotes corneal angiogenesis via its effects on VEGF-A, VEGF-C, and VEGF-D production. [17] MMP14 interacts with VEGFR1 and its enzymatic activity is essential for VEGFA-induced angiogenesis. IL-1 is a proinflammatory molecule produced by different cells, including fibroblasts, macrophages, and neutrophils, and induces the expression of adhesion molecules, chemokines, and growth factors that lead to neovascularization. [18]

Antiangiogenic factors can be categorized into endostatin/endostatin analogues (endostatin, neostatin, arresten, canstatin, and tumstatin), plasminogen/serine protease inhibitors (angiostatin and pigment epithelial-derived factor [PEDF]), and soluble VEGF receptors. [19,20,21,22]

Current management of corneal neovascularization

Corneal transplantation is at present the only successful universal treatment for this disease process.One therapeutic aim of these treatments is to initiate antiangiogenesis and stop the neoangiogenesis at early stages, whereas the other treatment modality aims to achieve angioregression by inducing reversion of immature vessels.

Corneal Transplantation

The analysis estimates that “presence of corneal neovascularization before surgery is 30% more likely that the transplant will fail, and more than doubles the risk of graft rejection”, in other words, the greater the neovascularization the higher risk of rejection.[23]

Treatment of Corneal Neovascularization- Laser/ Phototherapy

Argon laser therapy for corneal neovascularization is the use of an argon laser beam, which passes through a clear cornea, but, when there are many vessels present, the haemoglobin (within the blood) absorbs the argon energy allowing corneal vessels to coagulate, which causes reversal of the corneal neovascularization. [24] Studies have shown its efficacy in regression of corneal neovascularization. [25]Photodynamic therapy involves a photosensitizing compound, light and oxygen. The compound is absorbed by the neovascular tissue and is activated through laser treatment, which causes free radicals to be released thus destroying the surrounding neovascular tissue and reversing corneal neovascularization. [26] It has been shown that photodynamic therapy is safe and has a high efficacy within humans; however, it is a very costly method of treatment as well as time consuming.[26]

Both laser and phototherapy need further study to determine their

efficacy when compared to other therapeutic strategies. However, a recent study by Gerten et al. has shown that the combination therapy of bevacizumab with argon laser-therapy causes a marked decrease in corneal neovascularization, this being because the argon laser-induced coagulation closes the mature pathological blood vessels whilst the bevacizumab prevents new angiogenesis].[27]

Injections

Treatment can be administered in many ways, also including the administration of steroids and anti-VEGF agents through subconjunctival injections with similar efficacy to topical treatment.

Gene therapy involves transferring therapeutic genes to the cornea through different vectors. There are safety concerns regarding viral vectors (adenoviruses, retroviruses or lentiviruses) but they are the most efficient in infecting the corneal epithelial cells with infection rates of 80-100%, allowing higher gene transfer rates compared to non-viral vectors.[28]

Topical Treatments

Steroids and anti-VEGF agents are currently the mainstay initial treatment for corneal neovascularization. [29]Topical steroids such as cortisone, dexamethasone and prednisolone have all been shown to have an antiangiogenic effect and hence inhibit corneal neovasc ularization. However, there are studies suggesting that steroids do not inhibit the development of corneal vascularisation.[30] This was however demonstrated in response to corneal neovascularization post chemical injury, with recent research suggesting positive outcomes in other scenarios.[31]. It is thought that steroids work by inhibiting cell chemotaxis and by inhibiting pro-inflammatory cytokines like interleukin-1 and -6.[31] They also cause lymphocytes to be killed and inhibit vascular dilation, which all amounts to their antiangiogenic effect. The use of steroids (such as cortisone) in conjunction with heparin and cyclodextrins causes a greater antiangiogenic effect. Anti-VEGF drugs work by inhibiting VEGF which prevents new blood vessel formation through down regulation of endothelial cell proliferation. Bevacizumab is a humanized monoclonal antibody which binds to all VEGF isoforms.

CONCLUSION

The ever-expanding knowledge of the mechanisms involved in corneal neovascularization are allowing different treatment options to be developed. Anti-VEGF drugs have been the centre of discussion as have matrix-metalloproteinase inhibitors.

These methods of treatments for corneal neovascularization currently still depend on the blood vessel maturity stage. Therefore, local gene therapy may be a promising universal treatment of corneal neovascularization, with the hope that safety concerns can be allayed by continuing and impending research.

REFERENCES

1. Abdelfattah N. S., Amgad M., Zayed A. A., Salem H., Elkhanany A. E., Hussein H., El-Baky N. A. (2015). "Clinical correlates of common corneal neovascular diseases: a literature review". International Journal of Ophthalmology. 8 (1): 182.
2. Chang JH, Gabison EE, Kato T, Azar DT. Corneal neovascularization. Curr Opin Ophthalmol. 2001;12(4):242–249.
3. Abdelfattah NS, Amgad M, Zayed AA, Salem H, Elkhanany AE, Hussein H, Abd El-Baky N. Clinical correlates of common corneal neovascular diseases: A literature review. Int J Ophthalmol. 2015;8:182–1934.
4. Lee P, Wang CC, Adamis AP. Ocular neovascularization: an epidemiologic review. Surv Ophthalmol. 1998;43(3):245–269
5. Roshanadel D, Eslani M, Baradaran-Rafii A, Cheung AY, Kurji K, Jabbehdari S, Maiz A, Jalali S, Djalilian AR, Holland EJ. Current and emerging therapies for corneal neovascularization. Ocul Surf. 2018;16(4):398–414.
6. 6[4]Chiang, Homer; Hemmati, Houman (2013). "Treatment of Corneal Neovascularization". Ophthalmic Pearls: 35–36 – via Eyenet Magazine.
7. Chang JH, Garg NK, Lunde E, Han KY, Jain S, Azar DT. Corneal neovascularization: an anti-VEGF therapy review. Surv ophthalmol .2012. 57:415-29.
8. .Han KY, Chang JH, Lee H, Azar DT. Proangiogenic Interactions of Vascular Endothelial MMP14 With VEGF Receptor 1 in VEGFA-Mediated Corneal Angiogenesis. Invest Ophthalmol.Vis Sci 2016. 57:3313-22.
9. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor .
10. Mm Shibuya M. VEGF-VEGFR Signals in Health and Disease. Biomol Ther (Seoul). 2014;22:1–9
11. Cursiefen C, Chen L, Borges LP, Jackson D, Cao J, Radziejewski C, et al. VEGF-A stimulates lymphangiogenesis and hemangiogenesis in inflammatory neovascul arization via macrophage recruitment. J Clin Invest. 2004;113:1040–50.
12. Goldman J, Rutkowski JM, Shields JD, Pasquier MC, Cui Y, Schmökel HG, et al. Cooperative and redundant roles of VEGFR-2 and VEGFR-3 signaling in adult lymphangiogenesis. FASEB J. 2007;21:1003–12.
13. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. Genes Cancer. 2011;2:1097–105.
14. Kim WJ, Mohan RR, Mohan RR, Wilson SE. Effect of PDGF, IL-1alpha, and BMP2/4 on corneal fibroblast chemotaxis: expression of the platelet-derived growth factor system in the cornea. Invest Ophthalmol Vis Sci. 1999;40:1364–72.
15. Hoppenreijs VP, Pels E, Vrensen GF, Felten PC, Treffers WF. Platelet-derived growth factor: receptor expression in corneas and effects on corneal cells. Invest Ophthalmol Vis Sci. 1993;34:637–49.
16. Ellenberg D, Azar DT, Hallak JA, Tobaigy F, Han KY, Jain S, et al. Novel aspects of corneal angiogenic and lymphangiogenic privilege. Prog Retin Eye Res. 2010;29: 208–48.
17. Lu P, Li L, Liu G, Zhang X, Mukaida N. Enhanced experimental corneal neovascularization along with aberrant angiogenic factor expression in the absence of IL-1 receptor antagonist. Invest Ophthalmol Vis Sci. 2009;50:4761–8.
18. O'Reilly MS, Boehm T, Shing Y, Fukai N, Vasios G, Lane WS, et al. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. Cell. 1997;88:277–85.
19. Azar DT. Corneal angiogenic privilege: angiogenic and antiangiogenic factors in corneal avascularity, vasculogenesis, and wound healing (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc. 2006;104:264–302.
20. Ambati BK, Nozaki M, Singh N, Takeda A, Jani PD, Suthar T, et al. Corneal avascularity is due to soluble VEGF receptor-1. Natur 2006;443:993–7.
21. Albuquerque RJ, Hayashi T, Cho WG, Kleinman ME, Dridi S, Takeda A, et al. Alternatively spliced vascular endothelial growth factor receptor-2 is an essential endogenous inhibitor of lymphatic vessel growth. Nat Med. 2009;15:1023–30.
22. Bachmann B, Taylor RS, Cursiefen C. Corneal neovascularization as a risk factor for graft failure and rejection after keratoplasty: An evidence-based meta-analysis. Ophthalmology. 2010;117:1300–1305.
23. Reed JW, Fromer C, Klintworth GK. Induced corneal vascularization remission with argon laser therapy. Arch Ophthalmol. 1975;93:1017–1019.
24. Cherry PM, Faulkner JD, Shaver RP, Wise JB, Witter SL. Argon laser treatment of corneal neovascularization. Ann Ophthalmol. 1973;5:911–920.
25. Gomer CJ, Ferrario A, Hayashi N, Rucker N, Szirth BC, Murphree AL. Molecular, cellular, and tissue responses following photodynamic therapy. Lasers Surg Med. 1988;8:450–463.
26. Gerten G. Bevacizumab (avastin) and argon laser to treat neovascularization in corneal transplant surgery. Cornea. 2008;27:1195–1199.
27. Williams KA, Jessup CF, Coster DJ. Gene therapy approaches to prolonging corneal allograft survival. Expert Opin Biol Ther. 2004;4:1059–1071.]
28. Maddula S, Davis DK, Burrow MK, Ambati BK. Horizons in therapy for corneal angiogenesis. Ophthalmology. 2011;118:591–599.
29. Klintworth GK. Corneal angiogenesis a comprehensive critical review. New York: Springer; 1991.
30. Hoffart L, Matonti F, Conrath J, Daniel L, Ridings B, Masson GS, Chavane F. Inhibition of corneal neovascularization after alkali burn: Comparison of different doses of bevacizumab in monotherapy or associated with dexamethasone. Clin Experiment Ophthalmol. 2010;38:346–352.
31. Schleimer RP, Freeland HS, Peters SP, Brown KE, Derse CP. An assessment of the effects of glucocorticoids on degranulation, chemotaxis, binding to vascular endothelium and formation of leukotriene b4 by purified human neutrophils. J Pharmacol E