Chapter 4

# Corneal Angiogenesis: Etiologies, Complications, and Management

Sepehr Feizi

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66713

**Abstract**

A large subset of corneal pathologies involves the formation of new blood vessels, leading to compromised visual acuity. Additionally, neovascularization of the cornea worsens the prognosis of subsequent penetrating keratoplasty, keeping the patient in a vicious circle of poor prognosis. Ocular angiogenesis results from the upregulation of proangiogenic and downregulation of antiangiogenic factors. There is a tremendous need for developing effective measures to prevent and/or treat corneal neovascularization. Topical steroid medication, cautery, argon and yellow dye laser, and fine needle diathermy have all been advocated with varying degrees of success. The process of corneal neovascularization is primarily mediated by the vascular endothelial growth factor family of proteins, and current therapies are aimed at disrupting the various steps in this pathway. This article aims to review the clinical causes and presentations of corneal neovascularization caused by different etiologies. Moreover, this chapter reviews different complications caused by corneal neovascularization and summarizes the most relevant treatments available so far.

**Keywords:** cornea, angiogenesis, etiologies, complications, management

## 1. Introduction

A normal cornea is necessary to protect the eye against structural damage to the deeper ocular components as well as to provide a proper anterior refractive surface. Optimal vision and corneal clarity entail an avascular cornea, and maintaining the stromal avascularity is an important feature of the corneal pathophysiology. Corneal vascularization, which is a sign of corneal disease processes than a diagnosis, results from an imbalance between angiogenic and antiangiogenic factors [1]. The angiogenic factors stimulate the proliferation and migration of vascular endothelial cells, resulting in the formation of a capillary tube [2, 3]. Corneal

neovascularization is part of the natural healing processes, which are triggered by exposure of the cornea to trauma or pathogens, and is not necessarily 'harmful.' In the long-term and under certain circumstances, however, corneal neovascularization can surpass a threshold, invading the cornea, reducing visual acuity, and, in case of lamellar keratoplasty or penetrating keratoplasty, endangering corneal graft survival [4–7]. These complications have prompted clinicians to devise means to shut vessels. Topical steroid medication, cautery, argon and yellow dye laser, and fine needle diathermy (FND) have all been advocated with varying degrees of success. The advent of anti-vascular endothelial growth factor (VEGF) antibodies has resulted in a surge of interest in using these agents to treat corneal neovascularization. These approaches, however, have a limited clinical efficacy and can result in a multitude of undesirable complications. This chapter aims to review the causes, pathogenesis, and clinical presentations of corneal neovascularization caused by different etiologies, such as contact lens–induced keratitis, corneal ulcers, and herpes simplex stromal keratitis. Moreover, it reviews different complications caused by corneal neovascularization and summarizes the most relevant treatments available so far.

## 2. Etiologies

Corneal vascularization occurs as a nonspecific response to different clinical insults. Diseases associated with corneal neovascularization include corneal graft rejection, inflammatory disorders, chemical burns, contact lens–related hypoxia, stromal ulceration, infectious keratitis, limbal stem cell deficiency, and congenital disease (**Table 1**) [8–10].

| Categories | Cause |
|---|---|
| Infectious keratitis | Parasitic |
| | Viral |
| | Bacterial |
| | Fungal |
| Hypoxia | Contact lens wearing |
| Conjunctival/corneal degeneration | Pterygium |
| Inflammatory disorder | Stevens-Johnson syndrome |
| | Mucous membrane pemphigoid |
| | Corneal graft rejection |
| | Rosacea |
| | Atopic conjunctivitis |
| Ocular surface neoplasia | Conjunctival or corneal intraepithelial neoplasia |
| | Conjunctival or corneal squamous cell carcinoma |
| | Papilloma |
| Loss of limbal barrier function | Congenital (e.g., aniridia) |
| | Thermal burn, chemical burn, or other injury |

**Table 1.** Causes of corneal neovascularization.

http://dx.doi.org/10.5772/66713

Hypoxia related to contact lens wear is a common cause where corneal neovascularization is usually superficial and involves only the corneal periphery [11, 12]. However, if contact lens wear is not discontinued, deep stromal and central corneal invasion can take place.

Infections can result in corneal neovascularization with the patterns of response being different. Herpes simplex virus (HSV) keratitis is likely to cause extensive vascularization and lipid keratopathy, while, in Acanthamoeba keratitis, vascularization tends to develop late in the course of the disease (**Figure 1**). The continued presence of HSV-DNA and HSV-immune complexes

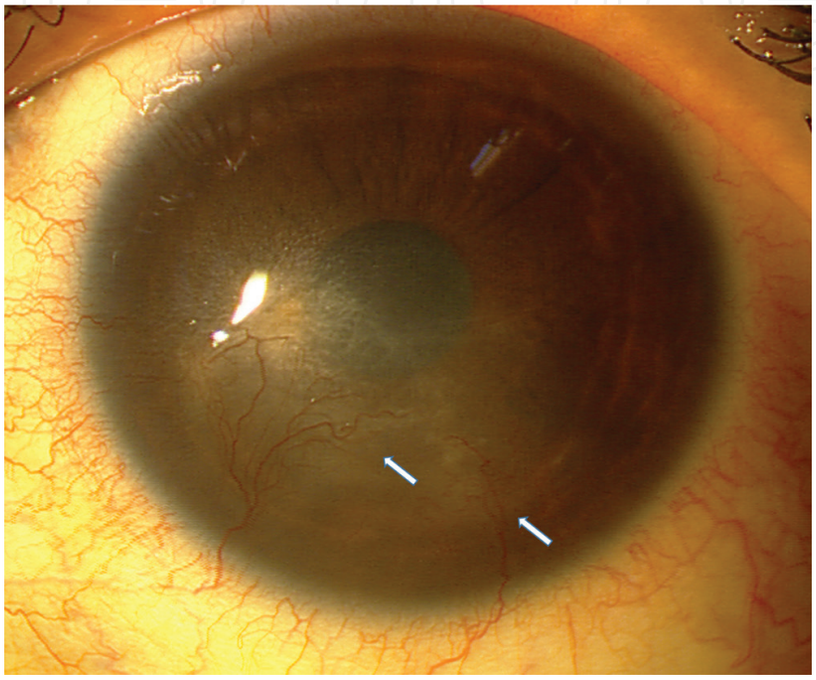

**Figure 1.** Acanthamoeba keratitis. Corneal opacity and vascularization (arrows) developed four months after corneal ulcer caused by Acanthamoeba in a contact lens wearer.

contributes to inflammation and angiogenesis in HSV stromal keratitis through increased levels of matrix metalloproteinase (MMP)-9 and vascular endothelial growth factor (VEGF) [13, 14]. There is a close link between extent (i.e., superficial or stromal) and location (i.e., central or peripheral) of infections, and the location and extent of corneal neovascularization.

Limbal stem cell deficiency (LSCD) occurs in a variety of ocular pathologies both congenital (e.g., aniridia) and acquired (e.g., contact lens use, drugs, chemical burns, etc.), which lead to partial or total loss of limbal stem cells [15, 16]. Chemical (acidic and alkaline) substances can penetrate and damage the cornea and anterior chamber, with alkali burns being more severe [17]. Conjunctivalization of the cornea with massive neovascularization may develop, leading to severe reductions in corneal clarity and visual acuity through the pannus formation on the cornea and an unstable and irregular epithelium [17, 18]. Deep vascularization may develop in the late healing phase following severe chemical burns (**Figure 2**).

Degenerative conditions such as pterygium are associated with corneal neovascularization that usually is accompanied with a fibrovascular pannus located on, rather than in, the corneal stroma. Long-standing irritation of the ocular surface such as in vernal keratoconjunctivitis can lead to aggressive corneal neovascularization (**Figure 3**).

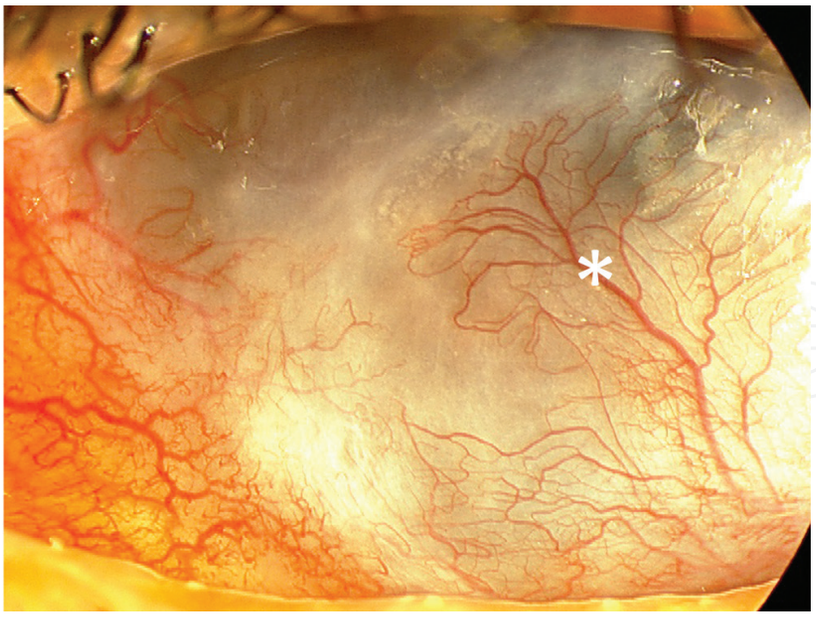

**Figure 2.** Limbal stem cell deficiency after alkali burn. The Figure demonstrates invasion of conjunctival vessels into the cornea (conjunctivalization) along with corneal stromal opacification and vascularization (asterisk).

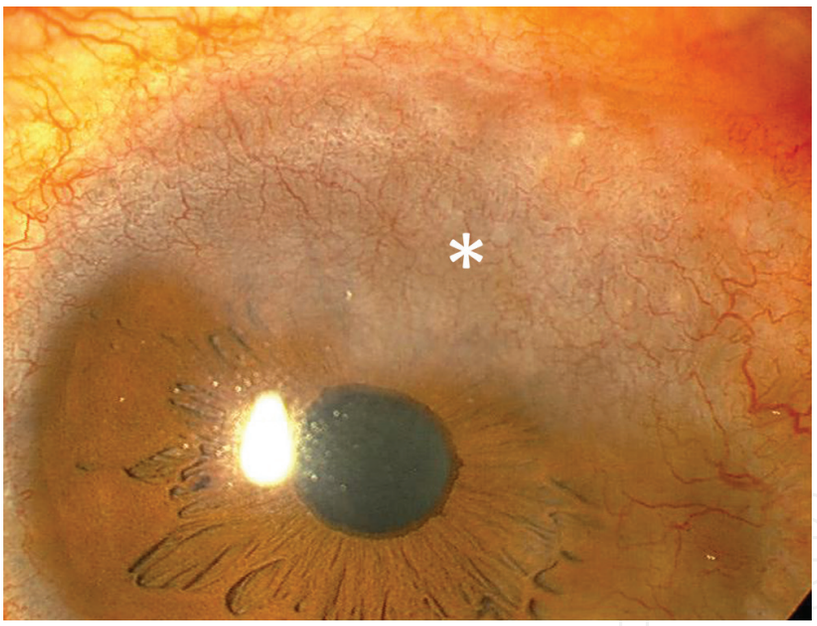

**Figure 3.** Corneal vascularization (asterisk) in a patient with vernal keratoconjunctivitis.

Ocular surface neoplasia, including papilloma and conjunctival/corneal intraepithelial neoplasia, can cause corneal neovascularization as part of the tumor angiogenic response. Initially, the vessels can be limited to the tumor but eventually invade the entire cornea. Other specific etiologies of corneal neovascularization include persistent corneal edema as in chronic hydrops of keratoconus and bullous keratopathy as well as corneal allograft rejection. Less common causes of corneal neovascularization are corneal foreign bodies and exposure to chemical toxins including mustard gas, radiation, or sun [19–21]. Intrastromal corneal ring implants, loose sutures, suture knots, and broken sutures seem to provide a stimulus for corneal vascularization

http://dx.doi.org/10.5772/66713

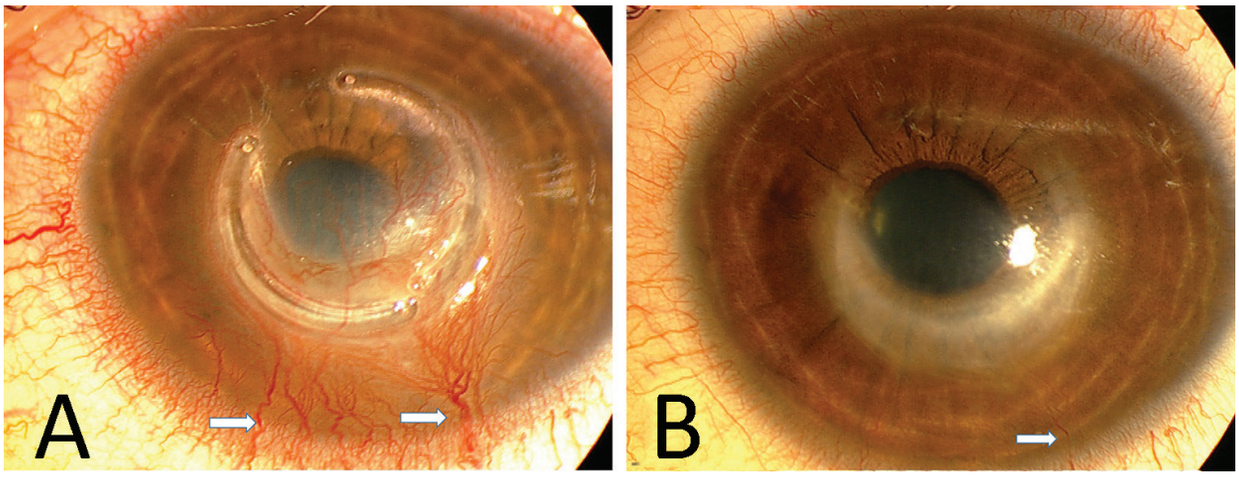


**Figure 4.** Intrastromal corneal ring segment implants complicated by corneal neovascularization. (A) Active young vessels (arrows) emanating from the limbus invade to the site of segment implantation. (B) The vessels have regressed after intrastromal corneal ring segment implants were removed. Partially regressed vessels are present in the inferior cornea (arrow).

(**Figure 4**). The mucus that collects around loose and broken sutures can trap polymorphonuclear cells and microbes inciting localized inflammation/infection, thus attracting vessels.

## 3. Pathogenesis

The upstream molecular pathway mechanisms resulting in corneal neovascularization differ in the different underlying pathologies. Nonetheless, core molecular pathways governing the processes of corneal hemangiogenesis seem to be shared among various conditions leading to the active stage of corneal neovascularization. The normally avascular cornea may vascularize in circumstances in which a disequilibrium between angiogenic and antiangiogenic stimuli results in a surplus of proangiogenic factors, such as VEGF, basic fibroblast growth factor (bFGF), interleukin-1 (IL-1), and MMP, and a deficiency in antiangiogenic agents, such as endostatin, angiostatin, and pigment epithelium-derived factor (PEDF) [22].

The so-called VEGF family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor [23]. VEGF-A is the most important member of this family, especially relating to pathologic hemangiogenesis through VEGF receptor (VEGFR)-2. VEGF-C and VEGF-D can stimulate lymphangiogenesis through VEGFR-2 and VEGFR-3, respectively [24, 25]. Macrophages, activated by injury or inflammation, can also produce VEGF-A, VEGF-C, and VEGF-D in corneal stroma [26]. VEGF-A sustains various steps of hemangiogenesis including vascular endothelial cell proliferation and migration, capillary lumen formation, and proteolytic activity [1]. The importance of VEGF-A in corneal neovascularization was exhibited experimentally on animal studies by inhibiting angiogenesis following stromal application of an anti-VEGF-A antibody [27].

Platelet-derived growth factors (PDGFs) are involved in cell division, growth, tissue remodeling, and angiogenesis. Receptors, such as PDGFR-a and PDGFR-b, and ligands, such as PDGF-A and PDGF-B, can be found in cornea and are associated with corneal

neovascularization [28, 29]. Improved understanding of the molecular mechanisms of vascularization has enabled identification of specific factors that suppress angiogenesis to maintain the avascularity of the cornea. Because several molecules are involved in corneal neovascularization, a multipronged approach is desirable.

## 4. Clinical presentations

Corneal neovascularization which arises from the limbus, conjunctiva, and iris can lead to a reduction in the clarity of the cornea and visual acuity because of edema, scarring, intracorneal lipid and protein deposition, and persistent inflammation. Additionally, there is a robust association between the presence of corneal neovascularization and corneal graft rejection with the risk increasing as more quadrants are affected by vessels (**Figure 5**) [4–7]. The presence of corneal neovascularization can also cause intraoperative bleeding, which can be associated with hyphema.

Abnormal vessels may invade the cornea at different planes depending on the location and nature of the inflammatory stimulus. Corneal neovascularization has three clinical patterns, based on the depth of involvement. The first type, superficial vascularization, results from ocular surface disease (**Figure 6**). The second type is stromal vessels, which results from alkaline injury or stromal keratitis (**Figure 7**). The third is deep vessels overlying Descemet's membrane, which can be associated with interstitial keratitis or HSV keratitis, or after deep anterior lamellar keratoplasty (**Figure 8**) [1, 8, 9, 22]. Mixed patterns are often observed clini-

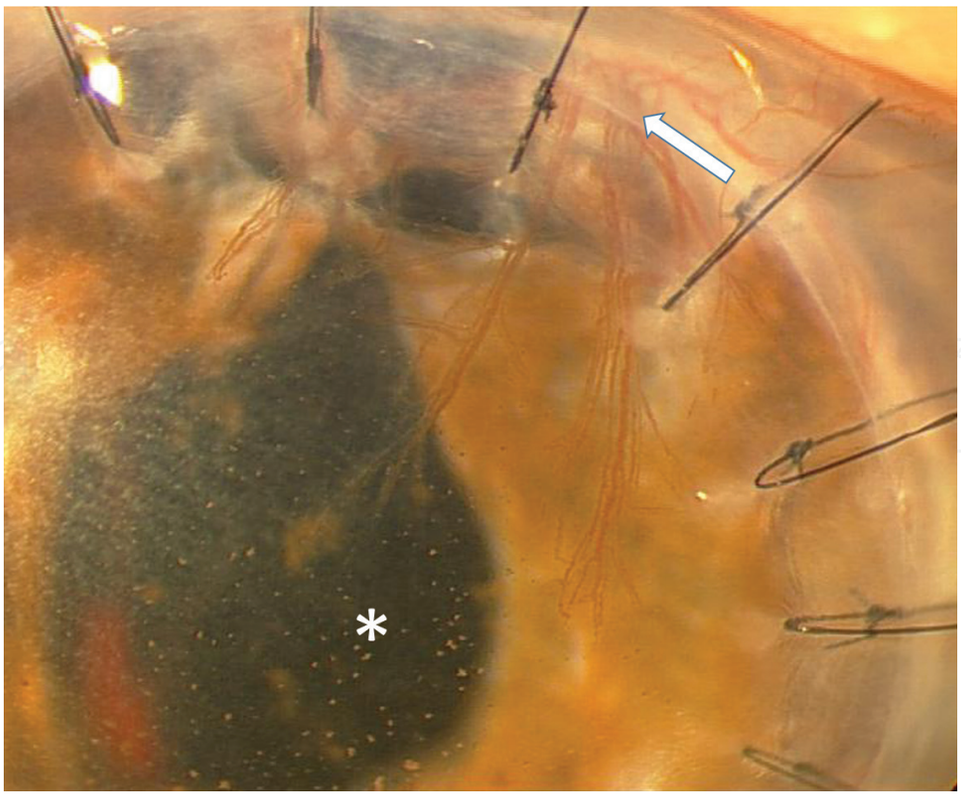


**Figure 5.** Endothelial corneal graft rejection in a high-risk graft. Active old corneal vessels (arrow) arising from the limbus sharply dip into a deep suture track and continue to the graft in an eye that underwent penetrating keratoplasty. The presence of keratic precipitates (asterisk) indicates an episode of endothelial graft rejection.

http://dx.doi.org/10.5772/66713

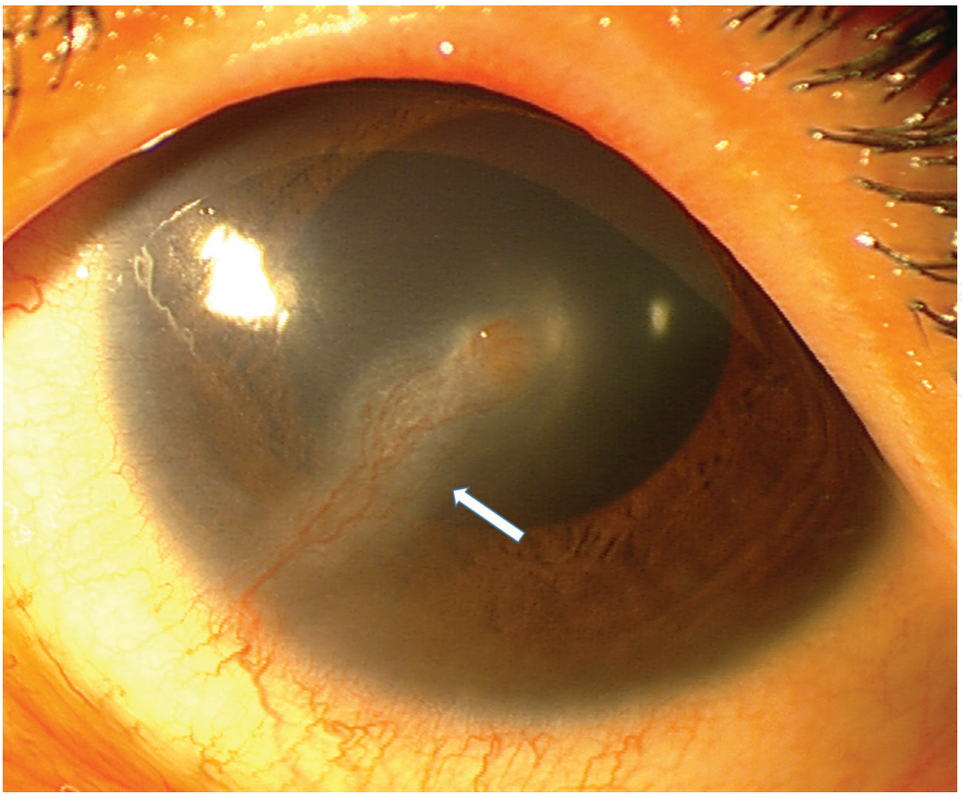

**Figure 6.** Phlyctenular keratitis. Superficial corneal vascularization (arrow) is evident in an eye with severe blepharitis. Adjacent stroma shows edema and infiltration.

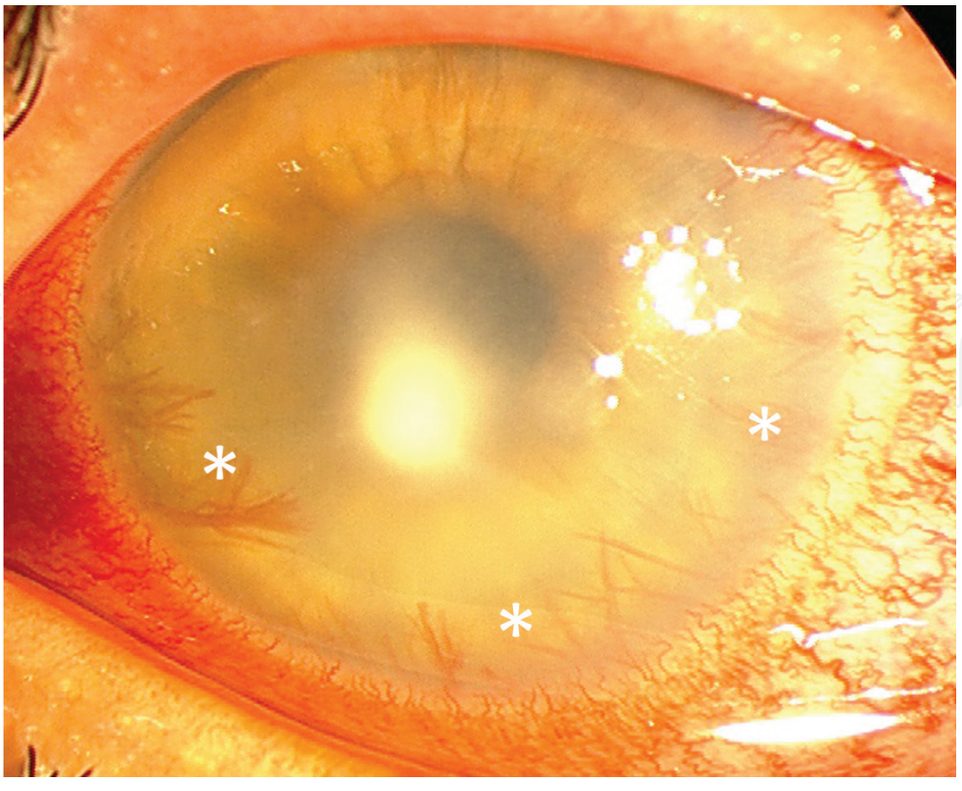

**Figure 7.** Deep stromal vascularization in an eye with recurrent herpes simplex stromal keratitis. Active young, bright red, brush-like vessels (asterisks) invade in to the corneal stroma.

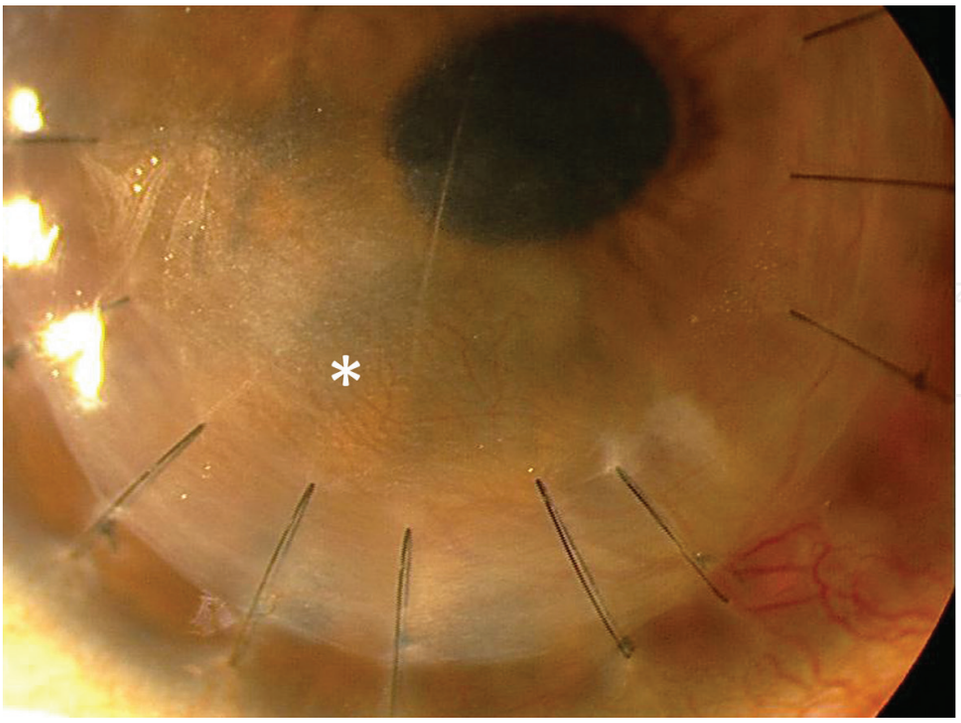

**Figure 8.** Partially regressed vessels with lipid keratopathy (asterisk) at the donor-recipient interface in a patient who underwent deep anterior lamellar keratoplasty (DALK). Vessels arising from the limbus sharply dip into a deep suture track and continue to the deep lamellar plane created by the DALK procedure, before fanning out. The vessels are dull red with a slow circulation, and some parts of the complex are less visible or have undergone attrition.

cally. The level of vascularization is chiefly related to the level of pathology rather than to the etiology. Superficial corneal pathology results in superficial vascularization, and deep pathology results in deep vessels. Often when the disease process extends through the thickness of the cornea, superficial and deep vessels are seen in the same cornea.

A detailed clinical evaluation of corneal neovascularization, including extension (the number of quadrants involved) and depth, is crucial for treatment planning. In addition to the extent and level of corneal vascularization, the state of vessel activity is also important [30]. Clinically, corneal vascularization can be classified as active young, active old, mature, partially regressed, and regressed. This often corresponds with the stage of activity or chronicity of the disease. Active young vessels are freshly formed vessels that are full of blood, appear bright red in color, have minimal surrounding fibrous tissue sheathing, and are actively progressing in the cornea with a well-defined arborizing network of fine (capillary) vessels (**Figures 4A** and **7**). The corneal stroma surrounding the vessels shows signs of leakage and edema. Active old vessels appear less bright and maintain a brisk circulation (**Figure 5**). This represents the stage when the vessels have reached and surrounded or covered the offending lesion in the cornea. Their progression ceases but consolidation continues. Mature vessels are relatively large vessels, with minimal arborization and regressed or absent capillary networks, seen to persist in scar tissue or in the corneal stroma after the corneal pathology has healed. These vessels contain blood and maintain a circulation (**Figure 9**). Partially regressed vessels are seen when the corneal pathology has abated in response to therapy or the arrival

http://dx.doi.org/10.5772/66713

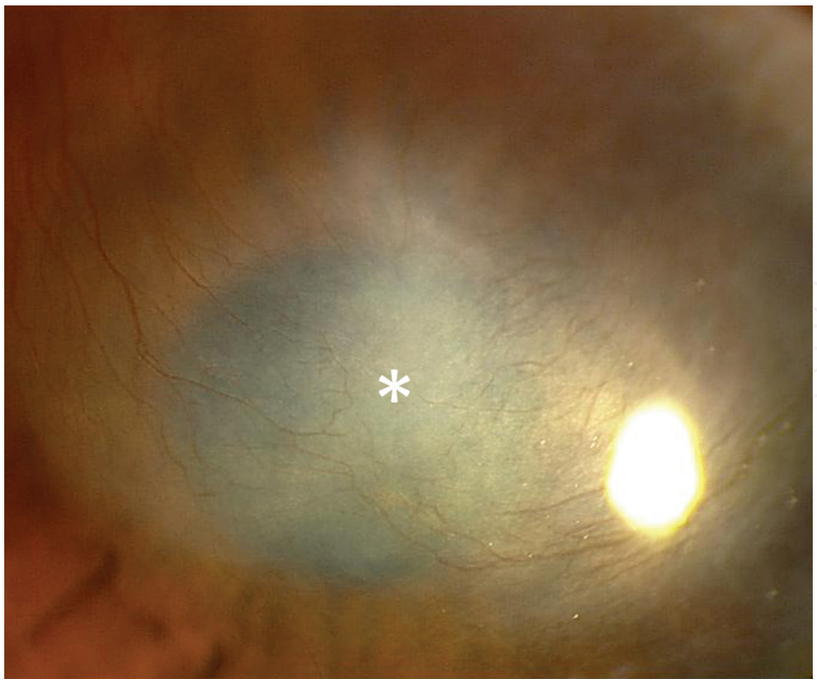


**Figure 9.** Mature vessels in the corneal stroma after the improvement of corneal ulcer (asterisk). The vessels are relatively large, with minimal arborization and regressed or absent capillary networks. These vessels which persist in scar tissue contain blood and maintain a circulation.

of corneal vessels. The circulation in the vascular complex is relatively slow, the vessels are less engorged, and some parts of the complex have become less visible or undergo attrition (**Figures 4B** and **8**). Regressed (ghost) vessels present as fine white lines mirroring the morphology of the original vessels. These do not have an active circulation, and the cornea where they are located is not edematous. Although clinically undetectable, lymphangiogenesis almost always accompanies hemangiogenesis in the cornea [31].

## 5. Paraclinical evaluation of corneal vascularization

Accurate evaluation and documentation of corneal neovascularization are essential to monitor the effect of any treatment modality employed. Case note entries can be used to assess the extent of corneal vascularization, and the depth of penetration and the centripetal progression of vessels, which allows a semiquantitative measurement of corneal neovascularization. It is neither time efficient nor practical, however, to manually trace the corneal vessels in each follow-up examination. Furthermore, the reproducibility is questionable, and the opportunity for variability and human error is very high.

The need to measure corneal neovascularization motivated researchers to explore measurement tools. An ideal measurement tool should allow rapid, reproducible, accurate, and objective measurement of corneal neovascularization. Digitized photographs with good contrast can be analyzed, based on the grayscale values, to evaluate the progression of vascularization [32]. Corneal vessels can be quantified on the basis of contrast enhancement, density threshold identification

for the blood vessels, and pixel measurement [33]. A more novel automatic approach on the basis of gray filter sampling and threshold analyses of digital photographs using an image analysis software has also been investigated [34, 35]. Despite the recent progress in the graphic editing software, automated methods have some limitations. First, the optimization and validation of any automated quantitative tool are questionable [36–38]. Second, it does not allow sufficient appreciation of details on vessel extent, localization, leakage, origin, and differentiation of the afferent and efferent systems. This information is of importance for guidance of clinical judgment and treatment [39].

Corneal angiography, using fluorescein and indocyanine green, provides excellent details of the neovascular complexes, thus enabling an enhanced clinical assessment and decision-making even in patients with complex corneal neovascularization [39]. The required technological equipment for corneal angiography is readily available in most ophthalmologic centers, as angiography is widely used to diagnose vascular disorders of the retina of various origin. It is a relatively inexpensive and safe diagnostic intervention, and serious adverse events like anaphylaxis to the intravenous dye are extremely rare [40, 41].

Fluorescein angiography gives an indication of the vessel maturity and leakage activity, whereas indocyanine green angiography allows better depiction of capillaries and deeper corneal neovascularization, particularly in the presence of vessel obscuration because of corneal haze and scarring [39]. It is possible to calculate the area of corneal neovascularization, the time to first detection of fluorescein dye leakage, corneal neovascular vessel diameter, and vascular tortuosity and activity. These parameters reliably quantify changes in corneal neovascularization over time [39]. Therefore, it allows monitoring of the natural course and treatment success [42].

## 6. Treatments

The treatment for corneal neovascularization aims at the occlusion of afferent corneal blood vessels to reduce exudative lipid keratopathy, and stromal edema and inflammation or as a preoperative conditioning intervention before keratoplasty to increase chances of graft survival [17, 43]. Current treatments for corneal neovascularization consist of topical nonsteroid anti-inflammatory and corticosteroid medications [44], photodynamic therapy [45], laser photocoagulation [46, 47], fine needle diathermy [48], and limbal, conjunctival, and amniotic membrane transplantation (AMT) [49]. More recently, manipulation of VEGF activity and manipulation of proangiogenic mediators like interleukin have been under investigation [50, 51]. Unfortunately, all of these approaches have a limited clinical efficacy, especially when the vessels are large because large vessels are difficult to occlude and easily recanalized. In addition, a multitude of undesirable side effects can occur after the treatment of corneal neovascularization. The following section reviews the available treatment approaches for corneal neovascularization and their limitations.

### 6.1. Corticosteroid therapy

Inflammation is a potent driver for corneal neovascularization. When inflammation settles, spontaneous regression of corneal neovascularization can occur and lead to gradual

http://dx.doi.org/10.5772/66713

resolution of lipid keratopathy if present. Topical and periocular steroids have been popular and can effectively reduce inflammation and consequently corneal neovascularization in various disease conditions. However, the risks of superinfection, glaucoma, and cataract associated with the long-term use of corticosteroids have been a limiting factor [44]. Additionally, steroids have only limited antiangiogenic effects [52]. Cyclosporine A and nonsteroidal anti-inflammatory agents were reported to be largely ineffective in controlling or limiting corneal angiogenesis [53].

### 6.2. Laser photocoagulation

Photocoagulation of vessels has been shown to be an effective method to obliterate corneal vascularization [46, 47]. The argon laser [46] and the 577 nm yellow dye lasers [47] have been used effectively for treating vascularization in lipid keratopathy and graft rejection. Laser obliteration of corneal efferent vessels is comparatively easy as they are wider and have a relatively slower blood flow. Conversely, the afferent vessels are narrower and deeper, have a rapid blood flow, and are more difficult to obliterate. Consequently, reopening of the afferent vessels takes place in a high proportion of patients. In such cases, the procedure can be repeated more than once. Laser photocoagulation may not be effective in cases with extensive corneal neovascularization [46]. Other drawbacks include damage to iris and accidental suture lysis, which has a significant implication for grafts with running sutures. Furthermore, the expense of this equipment and the lack of availability in most centers make the treatment inaccessible to most surgeons.

### 6.3. Fine needle diathermy

Fine needle diathermy (FND) is an inexpensive and useful procedure that can serve as an adjunct or alternative to laser photocoagulation for the management of established corneal vessels. FND is simple and inexpensive and can be performed under topical anesthesia by any ophthalmologist. It can be applied at any depth to obliterate both afferent and efferent vessels with equal efficacy. However, it may have to be repeated to obtain the desired result [48]. Corneal microperforation is a potentially serious adverse event that can occur during passage of the needle. This is particularly so when the vascularized cornea is thin [48]. Other adverse events, such as striae, whitening, and intracorneal hemorrhages, are reversible [48]. Transient opacification of the cornea is observed in the stroma immediately surrounding the needle in all patients and persists for 24–48 h, with complete resolution. Intracorneal hemorrhage occurring intraoperatively or immediately postoperatively is the commonest adverse event. Though dramatic in appearance, intracorneal hemorrhages all resolve over a week or two. Sometimes, crystalline deposits can develop in the site of hemorrhage [48].

### 6.4. Corneal anti-angiogenesis target therapies

The advent of anti-VEGF agents has introduced a new dimension to the management of corneal vessels [54]. Active young vessels which usually indicate an underlying ongoing pathology continuing to induce further vascularization are probably best treated with anti-VEGF drops or subconjunctival injections. There is a growing list of therapeutic agents that target corneal angiogenesis (**Table 2**). Currently, only limited experience using anti-VEGFs on the cornea and only in an off-label setting is available [54].

| Targets | Mechanisms | Therapeutics |
|---|---|---|
| Vascular endothelial growth factor | Anti–VEGF-A antibodies | Bevacizumab |
| | | Ranibizumab |
| | Soluble or modified VEGF receptors | VEGFR-2-Fc |
| | | sVEGFR-3 overexpression gene therapy |
| | | VEGFR-1 morpholino |
| | | Recombinant dimeric |
| | | sVEGFR-1 overexpression gene therapy |
| | | VEGFR intraceptor gene therapy (Flt23k, Flt24k) |
| | | Aflibercept/VEGF-Trap(R1R2) |
| | VEGF-A aptamer | Pegaptanib |
| Pigment epithelium-derived factor | PEDF direct effect | PEDF |
| | | PEDF gene therapy |
| | | PEDF-derived peptide |
| Angiostatin | Angiostatin direct effect | Angiostatin pump |
| Platelet-derived growth factor | Multitargeted receptor tyrosine kinase inhibitor | Sunitinib |
| | PDGF receptor inhibitor | AG 1296 |
| 12-Hydroxyeicosatrienoic acid | siRNA for cytochrome P450 mono-oxygenase | CYP4B1 siRNA gene therapy |
| Hypoxia-inducible factors | shRNA for hypoxia-inducible factors | HIF-1a shRNA gene therapy (HIF-1a RNAi-A) |
| Decorin | Decorin direct effect | Decorin gene therapy |
| Vascular adhesion protein | VAP-1/SSAO inhibitor | U-V002 |
| | | LJP1207 |
| Cannabinoid receptor CB1 | CB1 antagonist | Rimonabant |
| Vasohibin-1 | Vasohibin-1 directly effect | Vasohibin-1 gene therapy |

HIF-1a: hypoxia-inducible factor 1a, CYP: cytochrome P450 mono-oxygenase, PDGF: platelet-derived growth factor, SSAO: semicarbazide-sensitive amine oxidase, PEDF: pigment epithelium-derived factor, VAP-1: vascular adhesive protein-1, sVEGFR: soluble form of vascular endothelial growth factor receptor, VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor.

**Table 2.** Corneal antiangiogenesis target therapies.

http://dx.doi.org/10.5772/66713

*6.4.1. Anti-VEGF antibody*

Inhibition of VEGF activity by a specific neutralizing anti-VEGF antibody is one possible strategy for treating corneal angiogenesis. VEGF inhibitors such as pegaptanib sodium (Macugen™, OSI/Eyetech), off-label bevacizumab (Avastin™, Genentech), and ranibizumab (Lucentis™, Genentech) are currently used for the treatment of different retinal pathologies including wet-type age-related macular degeneration [55]. Both animal models and clinical trials have demonstrated that these agents are effective in reducing corneal neovascularization. Both ranibizumab and bevacizumab use the same mechanisms and nonspecifically inhibit the VEGF-A isoforms [56]. Nevertheless, differently from ranibizumab and bevacizumab, pegaptanib specifically binds to VEGF-A165 and does not inhibit all of the VEGF isoforms. Subconjunctival ranibizumab, pegaptanib sodium, and bevacizumab are effective with no epitheliopathy in reducing corneal angiogenesis. Repeated subconjunctival injections with higher doses and concentrations and combination therapy with other antiangiogenic agents may be valid options to improve the effectiveness of treatments [57].

Treating corneal new vessel with the anti-VEGF antibody has some limitations. In contrast to superficial and active vascularization, in which clear regression is observed, anti-VEGF agents have a lower effect on deep vascularization. The effect of the anti-VEGF antibodies depends on the time of the treatment after the onset of neovascularization. In contrast to newly formed vessels, stable vessels are less affected by VEGF blockade [58]. The vessels mature in chronic neovascularization, and pericytes are recruited to the area around the region of corneal neovascularization [59]. Such coverage may reduce the influence of anti-VEGF agents on the regression of newly formed immature vessels. Anti-VEGF therapy is only a symptomatic treatment of corneal neovascularization that does not cure the underlying pathology, making it necessary to repeat the treatment to maintain its positive effect over a span of time [27].

**Bevacizumab**, which is FDA approved for intravenous administration in the treatment of various cancers, is a full-length, humanized murine monoclonal antibody with a molecular weight of 149 kD. Bevacizumab recognizes all isoforms of VEGF and is in widespread use, off-label, as an intravitreal injection to treat different retinal diseases [60]. Additionally, studies have demonstrated that topical, subconjunctival, and intraocular application of bevacizumab can partially reduce corneal angiogenesis and inflammatory response, resulting in an increase in corneal transparency [61, 62]. Bevacizumab can inhibit macrophage migration to the corneal stroma in early but not late treatment. Macrophages are known to trigger neovascularization in ischemic or inflamed corneas [63]. There is a concern about the interference of the topical form but not subconjunctival form of bevacizumab with nerve regeneration and delayed wound healing [54, 64, 65].

**Ranibizumab**, which has VEGF-binding characteristics similar to bevacizumab, is a recombinant humanized monoclonal antibody fragment that binds and inhibits all VEGF-A isoforms. Bevacizumab and ranibizumab are related to each other, but ranibizumab is the Fab fragment from the same antibody used to create bevacizumab. Therefore, ranibizumab has a molecular weight of 48 kD, making it approximately one-third the size of bevacizumab and theoretically allowing a better corneal penetration. In addition, it has been affinity matured to optimize the VEGF-A binding potential. These characteristics may enable ranibizumab to reduce cor-

neal angiogenesis more effectively than bevacizumab [66]. Subconjunctival ranibizumab significantly reduces VEGF levels not only in the bulbar conjunctiva and cornea but also in the iris and aqueous humor [67]. Clinically, stable corneal neovascularization can be effectively treated by topical ranibizumab 1% as evidenced by a significant reduction in vessel caliber and neovascular area with no significant change in invasion area. These findings suggest that the main outcome of ranibizumab treatment for stable corneal neovascularization is to induce the narrowing of vessels more than a reduction in their length.

*6.4.2. Pigment epithelium-derived factor*

PEDF is a glycoprotein with neurotrophic, antitumorigenic, and antiangiogenic functions. PEDF can inhibit FGF, VEGF, and interlukin-8 (IL-8/CXCL8)-mediated angiogenesis by inducing the cells' apoptosis and reducing endothelial cell migration simultaneously [68, 69]. It is also found to play an important role in the antiangiogenic effect of AMT [70]. Topical PEDF or PEDF-derived (P5-2 and P5-3) peptides can downregulate VEGF expression and inhibit corneal neovascularization in a chemical-induced corneal model [71].

*6.4.3. Tyrosine kinase inhibitors*

Anti-VEGF antibodies block the effect of VEGF before it attaches to the endothelial receptors. Tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2) that is predominantly or exclusively expressed in endothelial cells is an important regulator of angiogenesis. Tyrosine kinase inhibitors inhibit the activity of VEGF by blocking tyrosine kinase in the intracellular part of the VEGF cell membrane receptor. This may offer a different opportunity for the management of the angiogenesis process in corneal diseases. Regorafenib is a multikinase inhibitor that targets various kinases, including PDGF β, VEGFR1, VEGFR2, and VEGFR3, mutant oncogenic kinases, TIE2, and the FGF receptor, which are involved in neovascularization. The inhibitory effects of topical regorafenib are comparable to those of topical bevacizumab and dexamethasone [72]. Sunitinib is a multitargeted receptor tyrosine kinase inhibitor that blocks both VEGF and PDGF. Topically administered sunitinib can reduce corneal neovascularization more effectively than bevacizumab [73].

Trastuzumab is a monoclonal antibody that interferes with the HER2/ neu receptor. Lapatinib is a dual tyrosine kinase inhibitor, which interrupts the epidermal growth factor receptor (EGFR) and HER2/ neu pathways. Lapatinib used in the form of lapatinib ditosylate is an orally active drug for solid tumors such as breast cancer. In recent studies, both substances were compared for the treatment of experimental corneal angiogenesis. The results suggested that systemically administered lapatinib is more effective than systemically administered trastuzumab in preventing corneal angiogenesis [74].

## 7. Conclusion

Corneal neovascularization is a common clinical feature in different corneal diseases including ocular traumatic or chemical injury, autoimmune diseases, chronic contact lens wear, infectious keratitis, and keratoplasties. Although corneal neovascularization can serve a

http://dx.doi.org/10.5772/66713

beneficial role in arresting stromal melts, wound healing, and the clearing of infections, its disadvantages are numerous and it frequently results in edema, tissue scarring, persistent inflammation, and lipid deposition that may significantly reduce vision. Furthermore, it plays a major role in corneal graft rejection by breaching corneal immune privilege. VEGF, which plays a crucial role in angiogenesis and the pathologic neovascularization associated with a variety of eye diseases, is the most important target for antiangiogenic therapies. Experience indicates that anti-VEGFs are effective in occluding actively growing corneal neovascularization but not established vessels. Surgical procedures, including laser photocoagulation or fine needle diathermy, are useful particularly to obliterate large, established corneal vessels.

## Author details

Sepehr Feizi

Address all correspondence to: sepehrfeizi@yahoo.com

Ophthalmic Research Center and Department of Ophthalmology, Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## References

[1] Chang JH, Gabison EE, Kato T, Azar DT. Corneal neovascularization. Curr Opin Ophthalmol 2001;12(4):242–249.

[2] Strömblad S, Cheresh DA. Integrins, angiogenesis and vascular cell survival. Chem Biol 1996;3(11):881–885.

[3] Lee HS, Chung SK. The effect of subconjunctival suramin on corneal neovascularization in rabbits. Cornea 2010;29(1):86–92.

[4] 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(7):1300–1305.

[5] Huang PT. Penetrating keratoplasty in infants and children. J AAPOS 2007;11(1):5–6.

[6] Panda A, Vanathi M, Kumar A, Dash Y, Priya S. Corneal graft rejection. Surv Ophthalmol 2007;52(4):375–396.

[7] Sellami D, Abid S, Bouaouaja G, Ben Amor S, Kammoun B, Masmoudi M, Dabbeche K, Boumoud H, Ben Zina Z, Feki J. Epidemiology and risk factors for corneal graft rejection. Transplant Proc 2007;39(8):2609–2611.

[8] Menzel-Severing J. Emerging techniques to treat corneal neovascularisation. Eye (Lond) 2012;26(1):2–12.

[9] Tshionyi M, Shay E, Lunde E, Lin A, Han KY, Jain S, Chang JH, Azar DT. Hemangiogenesis and lymphangiogenesis in corneal pathology. Cornea 2012;31(1):74–80.

[10] Beebe DC. Maintaining transparency: a review of the developmental physiology and pathophysiology of two avascular tissues. Semin Cell Dev Biol 2008;19(2):125–133.

[11] Madigan MC, Penfold PL, Holden BA, Billson FA. Ultrastructural features of contact lens-induced deep corneal neovascularization and associated stromal leukocytes. Cornea 1990;9(2):144–1451.

[12] Wong AL, Weissman BA, Mondino BJ. Bilateral corneal neovascularization and opacification associated with unmonitored contact lens wear. Am J Ophthalmol 2003;136(5):957–958.

[13] Remeijer L, Duan R, van Dun JM, Wefers Bettink MA, Osterhaus AD, Verjans GM. Prevalence and clinical consequences of herpes simplex virus type 1 DNA in human cornea tissues. J Infect Dis 2009;200(1):11–19.

[14] Hayashi K, Hooper LC, Detrick B, Hooks JJ. HSV immune complex (HSV-IgG: IC) and HSV-DNA elicit the production of angiogenic factor VEGF and MMP-9. Arch Virol 2009;154(2):219–226.

[15] Dua HS, Azuara-Blanco A. Limbal stem cells of the corneal epithelium. Surv Ophthalmol 2000;44(5):415–425.

[16] Kokotas H, Petersen MB. Clinical and molecular aspects of aniridia. Clin Genet 2010;77(5):409–420.

[17] Lee P, Wang CC, Adamis AP. Ocular neovascularization: an epidemiologic review. Surv Ophthalmol 1998;43(3):245–269.

[18] Mochimaru H, Usui T, Yaguchi T, Nagahama Y, Hasegawa G, Usui Y, Shimmura S, Tsubota K, Amano S, Kawakami Y, Ishida S. Suppression of alkali burn-induced corneal neovascularization by dendritic cell vaccination targeting VEGF receptor 2. Invest Ophthalmol Vis Sci 2008;49(5):2172–2177.

[19] Applegate LA, Ley RD. DNA damage is involved in the induction of opacification and neovascularization of the cornea by ultraviolet radiation. Exp Eye Res 1991;52(4):493–497.

[20] Cogan DG. Corneal vascularization. Invest Ophthalmol Vis Sci 1962;1:253–261.

[21] Javadi MA, Jafarinasab MR, Feizi S, Karimian F, Negahban K. Management of mustard gas-induced limbal stem cell deficiency and keratitis. Ophthalmology 2011;118(7):1272–1281.

[22] Chang JH, Garg NK, Lunde E, Han KY, Jain S, Azar DT. Corneal neovascularization: an anti-VEGF therapy review. Surv Ophthalmol 2012;57(5):415–429.

[23] Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J 1999;13(1):9–22.

[24] Goldman J, Rutkowski JM, Shields JD, Pasquier MC, Cui Y, Schmökel HG, Willey S, Hicklin DJ, Pytowski B, Swartz MA. Cooperative and redundant roles of VEGFR-2 and VEGFR-3 signaling in adult lymphangiogenesis. FASEB J 2007;21(4):1003–1012.

[25] 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(12):1097–1105.

[26] Cursiefen C, Chen L, Borges LP, Jackson D, Cao J, Radziejewski C, D'Amore PA, Dana MR, Wiegand SJ, Streilein JW. VEGF-A stimulates lymphangiogenesis and hemangiogenesis in inflammatory neovascularization via macrophage recruitment. J Clin Invest 2004;113(7):1040–1050.

[27] Krizova D, Vokrojova M, Liehneova K, Studeny P. Treatment of corneal neovascularization using Anti-VEGF bevacizumab. J Ophthalmol. 2014;2014:178132. doi:10.1155/2014/178132.

[28] 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(7):1364–1372.

[29] 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(3):637–649.

[30] Pillai CT, Dua HS, Hossain P. Fine needle diathermy occlusion of corneal vessels. Invest Ophthalmol Vis Sci 2000;41(8):2148–2153.

[31] Cursiefen C, Chen L, Dana MR, Streilein JW. Corneal lymphangiogenesis: evidence, mechanisms, and implications for corneal transplant immunology. Cornea 2003;22(3):273–281.

[32] Proia AD, Chandler DB, Haynes WL, Smith CF, Suvarnamani C, Erkel FH, Klintworth GK. Quantitation of corneal neovascularization using computerized image analysis. Lab Invest 1988;58(4):473–479.

[33] Conrad TJ, Chandler DB, Corless JM, Klintworth GK. In vivo measurement of corneal angiogenesis with video data acquisition and computerized image analysis. Lab Invest 1994;70(3):426–434.

[34] Bock F, König Y, Kruse F, Baier M, Cursiefen C. Bevacizumab (Avastin) eye drops inhibit corneal neovascularization. Graefes Arch Clin Exp Ophthalmol 2008;246(2):281–284.

[35] Cursiefen C, Bock F, Horn FK, Kruse FE, Seitz B, Borderie V, Früh B, Thiel MA, Wilhelm F, Geudelin B, Descohand I, Steuhl KP, Hahn A, Meller D. GS-101 antisense oligonucleotide eye drops inhibit corneal neovascularization: interim results of a randomized phase II trial. Ophthalmology 2009;116(9):1630–1637.

[36] Wu PC, Liu CC, Chen CH, Kou HK, Shen SC, Lu CY, Chou WY, Sung MT, Yang LC. Inhibition of experimental angiogenesis of cornea by somatostatin. Graefes Arch Clin Exp Ophthalmol 2003;241(1):63–69.

[37] You IC, Kang IS, Lee SH, Yoon KC. Therapeutic effect of subconjunctival injection of bevacizumab in the treatment of corneal neovascularization. Acta Ophthalmol 2009;87(6):653–658.

[38] Jhanji V, Liu H, Law K, Lee VY, Huang SF, Pang CP, Yam GH. Isoliquiritigenin from licorice root suppressed neovascularisation in experimental ocular angiogenesis models. Br J Ophthalmol 2011;95(9):1309–1315.

[39] Kirwan RP, Zheng Y, Tey A, Anijeet D, Sueke H, Kaye SB. Quantifying changes in corneal neovascularization using fluorescein and indocyanine green angiography. Am J Ophthalmol 2012;154(5):850–858.

[40] Kwan AS, Barry C, McAllister IL, Constable I. Fluorescein angiography and adverse drug reactions revisited: the Lions Eye experience. Clin Experiment Ophthalmol 2006;34(1):33–38.

[41] Hope-Ross M, Yannuzzi LA, Gragoudas ES, Guyer DR, Slakter JS, Sorenson JA, Krupsky S, Orlock DA, Puliafito CA. Adverse reactions due to indocyanine green. Ophthalmology 1994;101(3):529–533.

[42] Steger B, Romano V, Kaye SB. Corneal indocyanine green angiography to guide medical and surgical management of corneal neovascularization. Cornea 2016;35(1):41–45.

[43] Romano V, Spiteri N, Kaye SB. Angiographic-guided treatment of corneal neovascularization. JAMA Ophthalmol 2015;133(3):e143544.

[44] Al-Torbak A, Al-Amri A, Wagoner MD. Deep corneal neovascularization after implantation with intrastromal corneal ring segments. Am J Ophthalmol 2005;140(5):926–927.

[45] Brooks BJ, Ambati BK, Marcus DM, Ratanasit A. Photodynamic therapy for corneal neovascularisation and lipid degeneration. Br J Ophthalmol 2004;88(6):840.

[46] Baer JC, Foster CS. Corneal laser photocoagulation for treatment of neovascularization. Efficacy of 577 nm yellow dye laser. Ophthalmology 1992;99(2):173–179.

[47] L'sEsperance FA Jr. Clinical photocoagulation with organic dye laser. A preliminary communication. Arch Ophthalmol 1985;103(9):1312–1316.

[48] Faraj LA, Elalfy MS, Said DG, Dua HS. Fine needle diathermy occlusion of corneal vessels. Br J Ophthalmol 2014;98(9):1287–1290.

[49] Liang L, Li W, Ling S, Sheha H, Qiu W, Li C, Liu Z. Amniotic membrane extraction solution for ocular chemical burns. Clin Exp Ophthalmol 2009;37(9):855–863.

[50] Oliveira HB, Sakimoto T, Javier JA, Azar DT, Wiegand SJ, Jain S, Chang JH. VEGF Trap(R1R2) suppresses experimental corneal angiogenesis. Eur J Ophthalmol 2010;20(1):48–54.

[51] Hos D1, Bock F, Dietrich T, Onderka J, Kruse FE, Thierauch KH, Cursiefen C. Inflammatory corneal (lymph) angiogenesis is blocked by VEGFR-tyrosine kinase inhibitor ZK 261991, resulting in improved graft survival after corneal transplantation. Invest Ophthalmol Vis Sci 2008;49(5):1836–1842.

[52] Cursiefen C, Wenkel H, Martus P, Langenbucher A, Nguyen NX, Seitz B, Küchle M, Naumann GO. Impact of short-term versus long-term topical steroids on corneal neovascularization after non-high-risk keratoplasty. Graefes Arch Clin Exp Ophthalmol 2001;239(7):514–521.

[53] Ey RC, Hughes WF, Bloome MA, Tallman CB. Prevention of corneal vascularization. Am J Ophthalmol 1968;66(6):1118–1131.

[54] Dastjerdi MH, Al-Arfaj KM, Nallasamy N, Hamrah P, Jurkunas UV, Pineda R 2nd, Pavan-Langston D, Dana R. Topical bevacizumab in the treatment of corneal neovascularization: results of a prospective, open-label, noncomparative study. Arch Ophthalmol 2009;127(4):381–389.

[55] Heier JS, Antoszyk AN, Pavan PR, Leff SR, Rosenfeld PJ, Ciulla TA, Dreyer RF, Gentile RC, Sy JP, Hantsbarger G, Shams N. Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/ II multicenter, controlled, multidose study. Ophthalmology 2006;113(4):633.e1–4.

[56] Bhisitkul RB. Vascular endothelial growth factor biology: clinical implications for ocular treatments. Br J Ophthalmol 2006;90(12):1542–1547.

[57] Akar EE, Oner V, Küçükerdönmez C, Aydın Akova Y. Comparison of subconjunctivally injected bevacizumab, ranibizumab, and pegaptanib for inhibition of corneal neovascularization in a rat model. Int J Ophthalmol 2013;6(2):136–140.

[58] Ferrari G, Dastjerdi MH, Okanobo A, Cheng SF, Amparo F, Nallasamy N, Dana R. Topical ranibizumab as a treatment of corneal neovascularization. Cornea 2013;32(7):992–997.

[59] Cursiefen C, Hofmann-Rummelt C, Küchle M, Schlötzer-Schrehardt U. Pericyte recruitment in human corneal angiogenesis: an ultrastructural study with clinicopathological correlation. Br J Ophthalmol 2003;87(1):101–106.

[60] Keating AM, Jacobs DS. Anti-VEGF treatment of corneal neovascularization. Ocul Surf 2011;9(4):227–237.

[61] Avisar I, Weinberger D, Kremer I. Effect of subconjunctival and intraocular bevacizumab injections on corneal neovascularization in a mouse model. Curr Eye Res 2010;35(2):108–115.

[62] Lee SH, Leem HS, Jeong SM, Lee K. Bevacizumab accelerates corneal wound healing by inhibiting TGF-beta2 expression in alkali-burned mouse cornea. BMB Rep 2009;42(12):800–805.

[63] Chen WL, Chen YM, Chu HS, Lin CT, Chow LP, Chen CT, Hu FR. Mechanisms controlling the effects of bevacizumab (avastin) on the inhibition of early but not late formed corneal neovascularization. PLoS One 2014;9(4):e94205. doi:10.1371/journal.pone.0094205.

[64] Kim TI, Chung JL, Hong JP, Min K, Seo KY, Kim EK. Bevacizumab application delays epithelial healing in rabbit cornea. Invest Ophthalmol Vis Sci 2009;50(10):4653–4659.

[65] Koenig Y, Bock F, Horn F, Kruse F, Straub K, Cursiefen C. Short- and long-term safety profile and efficacy of topical bevacizumab (Avastin) eye drops against corneal neovascularization. Graefes Arch Clin Exp Ophthalmol 2009;247(10):1375–1382.

[66] Stevenson W, Cheng SF, Dastjerdi MH, Ferrari G, Dana R. Corneal neovascularization and the utility of topical VEGF inhibition: ranibizumab (Lucentis) vs bevacizumab (Avastin). Ocul Surf 2012;10(2):67–83.

[67] Liarakos VS, Papaconstantinou D, Vergados I, Douvali M, Theodossiadis PG. The effect of subconjunctival ranibizumab on corneal and anterior segment neovascularization: study on an animal model. Eur J Ophthalmol 2014;24(3):299–308.

[68] Duh EJ, Yang HS, Suzuma I, Miyagi M, Youngman E, Mori K, Katai M, Yan L, Suzuma K, West K, Davarya S, Tong P, Gehlbach P, Pearlman J, Crabb JW, Aiello LP, Campochiaro PA, Zack DJ. Pigment epithelium-derived factor suppresses ischemia-induced retinal neovascularization and VEGF-induced migration and growth. Invest Ophthalmol Vis Sci 2002;43(3):821–829.

[69] Mori K, Gehlbach P, Ando A, McVey D, Wei L, Campochiaro PA. Regression of ocular neovascularization in response to increased expression of pigment epithelium-derived factor. Invest Ophthalmol Vis Sci 2002;43(7):2428–2434.

[70] Shao C, Sima J, Zhang SX, Jin J, Reinach P, Wang Z, Ma JX. Suppression of corneal neovascularization by PEDF release from human amniotic membranes. Invest Ophthalmol Vis Sci 2004;45(6):1758–1762.

[71] Jin J, Ma JX, Guan M, Yao K. Inhibition of chemical cautery-induced corneal neovascularization by topical pigment epithelium-derived factor eyedrops. Cornea 2010;29(9):1055–1061.

[72] Onder HI, Erdurmus M, Bucak YY, Simavli H, Oktay M, Kukner AS. Inhibitory effects of regorafenib, a multiple tyrosine kinase inhibitor, on corneal neovascularization. Int J Ophthalmol 2014;7(2):220–225.

[73] Pérez-Santonja JJ1, Campos-Mollo E, Lledó-Riquelme M, Javaloy J, Alió JL. Inhibition of corneal neovascularization by topical bevacizumab (Anti-VEGF) and sunitinib (Anti-VEGF and Anti-PDGF) in an animal model. Am J Ophthalmol 2010;150(4):519–528.

[74] Kaya MK, Demir T, Bulut H, Akpolat N, Turgut B. Effects of lapatinib and trastuzumab on vascular endothelial growth factor in experimental corneal neovascularization. Clin Exp Ophthalmol 2015;43(5):449–457.