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An Overview on Treatment of Corneal Neovascularization

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Abstract:

Corneal neovascularization (CN) is a pathological process characterized by the invasion of new blood vessels into the normally avascular cornea, leading to loss of corneal transparency, chronic inflammation, lipid deposition, and potential visual impairment. It commonly develops secondary to inflammation, infection, hypoxia, trauma, limbal stem cell deficiency, or corneal transplantation. CN represents a major risk factor for graft rejection and poor visual outcomes. Over the past years, advances in the understanding of angiogenic mechanisms have led to the development of multiple medical and surgical treatment modalities targeting both newly formed and mature corneal vessels.

Keywords: Corneal neovascularization; Anti-VEGF therapy; Angiogenesis; Fine needle diathermy; Photodynamic therapy; Limbal stem cell transplantation.

Introduction:

The cornea is a transparent, avascular tissue, and preservation of its avascularity is essential for maintaining optical clarity and visual acuity. Corneal neovascularization (CN) occurs when the balance between pro-angiogenic and anti-angiogenic factors is disrupted, leading to the invasion of new blood vessels from the limbal vascular plexus into the corneal stroma. This pathological process is commonly triggered by inflammation, infection, hypoxia, trauma, chemical burns, contact lens wear, limbal stem cell deficiency, and corneal transplantation. Clinically, CN is associated with stromal scarring, lipid deposition, chronic inflammation, and significant visual impairment, and it represents a major risk factor for corneal graft rejection and failure (1).

At the molecular level, corneal angiogenesis is regulated by a complex interaction between angiogenic mediators such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and inflammatory cytokines, and endogenous anti-angiogenic factors including pigment epithelium-derived factor (PEDF) and angiostatin. Newly formed immature corneal vessels are highly dependent on VEGF signaling, making them susceptible to pharmacological inhibition. In contrast, mature vessels covered by pericytes show reduced dependence on VEGF and are more resistant to medical therapy alone. This biological distinction has important therapeutic implications and explains the variable response of CN to different treatment modalities (2).

Management strategies for corneal neovascularization can be broadly divided into angiostatic anti-angiogenic therapies, which aim to prevent the growth of new vessels, and angioregressive or angio-occlusive approaches, which target established pathological vessels. Medical treatments include corticosteroids, anti-VEGF agents, immunosuppressive drugs, and antisense oligonucleotides, while interventional options encompass fine needle diathermy, laser photocoagulation, photodynamic therapy, and novel techniques such as mitomycin intravascular chemoembolization. In advanced or refractory cases, ocular surface reconstruction and corneal transplantation may be required. A comprehensive understanding of the underlying mechanisms of CN is therefore essential for selecting the most appropriate therapeutic approach and optimizing clinical outcomes (3).

Therapeutic approaches in CN can be classified into: Angiostatic antiangiogenic approach to inhibit the outgrowths of newly formed immature vessels, and Angioregressive/angioocclusive approach to help in

regression of already formed mature pathologic vessels. Mature vessels with pericyte-covering do not depend on VEGF and other angiogenic growth factors for their growth, so additional physical procedures are needed to close these mature vessels **(2).**

Table 1 : Anti-angiogenic treatments and their mechanisms of action **(2).**

Anti-angiogenic factor	**Mechanism of action**
Ranibizumab	Monoclonal antibody fragment for VEGFA.
Bevacizumab	Monoclonal antibody for VEGFA.
Pegaptanib	RNA aptamer against VEGF165.
Aflibercept	Soluble decoy receptor for VEGFA and PGF.
Triamcinolone acetonide	Corticosteroid inhibiting inflammatory response.
Sunitinib	Inhibitor of receptor tyrosine kinases.
GS-101	Oligonucleotid against insulin receptor-1.
Doxycycline/Triamcinolone Combination	MMP-2 inhibition.
Cyclosporin A	Reduction in IL-2 induced corneal NV.
Methotrexate	Possible inhibition macrophage infiltration and endothelial cell proliferation.
Tacrolimus	Inhibits T-lymphocyte signal, IL-2 transcription.
PEDF	Endogenous angiogenic inhibitor.
Argon laser	Ablate neovessels.
Photodynamic therapy	Vaso-occlusion of corneal vessels.

A- Angiostatic antiangiogenic approach

GS101/aganirsen, topical steroids/cyclosporine A, and anti-VEGFs are among the medications used to block active corneal angiogenesis.

1. Steroids: According to Cursiefen et al. (4), corticosteroids are the usual medical treatment for individuals with actively expanding CN, especially in cases of CN linked to corneal transplantation.By reducing the inflow of inflammatory cells, the expression of proinflammatory cytokines (such as IL-1 and IL-6), and the release of arachidonic acid, corticosteroids prevent angiogenesis. Steroids vary greatly in their anti-hemangiogenic and anti-lymphangiogenic potencies; the most effective anti-lymphangiogenic medications are prednisolone and dexamethasone. Therefore, in order to prevent rejection, prednisolone should be used in corneal transplant cases. While corticosteroids are often unsuccessful in treating stable CN, they may inhibit the development of inflammation-induced CN. Steroids are linked to serious long-term side effects, including as cataract, ocular hypertension, corneal thinning, and opportunistic infections, despite their partial anti-angiogenic impact. Therefore, to increase safety and efficacy, more specialized anti-angiogenic medications are required. Indeed, in experimental CN models, the strongest anti-angiogenic impact was obtained by a combination anti-inflammatory and anti-angiogenic treatment approach (e.g., by combining steroids and contemporary anti-VEGFs) (5).

2. Anti-VEGF Treatment:Bevacizumab eye drops significantly improve the condition of CN patients who are not responding to steroid treatment. According to reports, subconjunctival injections and anti-VEGF eye drops are

safe and efficient ways to treat corneal angiogenesis (6). Experimental CN is strongly inhibited by anti-VEGF pharmaceutical approaches employing bevacizumab, ranibizumab, pegaptanib, or VEGF-Trap. The majority of research and clinical procedures employ bevacizumab because it is more economical, however ranibizumab has a lower molecular weight than bevacizumab, which enables more quick and efficient penetration to ocular surfaces.

Bevacizumab is a full-length, recombinant, humanized anti-VEGF monoclonal antibody (IgG1) that is sold commercially. According to Block et al. (7), it binds to and inhibits sVEGF (VEGF-A type), which stops it from attaching to the receptor and stops endothelial cell proliferation and vascular development, which in turn stops angiogenesis.Bevacizumab treatment for Stevens-Johnson syndrome, corneal transplant rejection, recurrent pterygium, and herpetic keratitis demonstrated encouraging outcomes when applied topically and subconjunctivally (8).

Administration routes and dose

Topical application: Bevacizumab, when applied topically, is safe and efficacious against both established and actively forming new corneal vasculature.Numerous animal studies have demonstrated the effectiveness of anti-VEGF treatment.In rat models, topical bevacizumab (4 mg/ml) administered twice daily for one week decreased chemically induced CN. Anti-VEGF therapy may be used as an adjuvant or substitute for traditional medications in the treatment of stable CN, as evidenced by the notable decrease in NA and narrowing of corneal blood vessel diameter in response to topical anti-VEGF therapy (9). Subconjunctival injection: Research has demonstrated that subconjunctival delivery of anti-VEGF is more effective than topical instillation in the management of CN. Compared to topical treatment, subconjunctival injections provide slower tissue release and higher intraocular concentrations. Anti-VEGF has thus been shown to diffuse into the corneal stroma following subconjunctival therapy and stay there for a few days (5).

NV is more effectively slowed by subconjunctival injections than by topical administration. Topical application is further hampered by a number of factors, including low stability in solution, limited penetration through intact epithelial barriers, and formulation complexity, which increases the risk of bioactivity loss over extended storage (10). Early treatment with weekly subconjunctival bevacizumab administration at a dose of 2.5 mg/0.1 ml for one month has been shown to inhibit and regress CN; however, late treatment with bevacizumab administration at the same dose and duration after triggering NV for one month has a lower anti-angiogenic effect on corneal vessels that are actively growing (11).

Anti-VEGF adverse effects on the surface of the eyes:Anti-VEGF treatments are generally safe to use in clinical settings in CN, although a number of side effects have been noted. The physiological actions of VEGF on the surface of the eye that are known to be "non-angiogenic" are the cause of these possible adverse consequences.

1. Neurotrophic keratopathy: One of the human body's most innervated tissues is the cornea. Normal avascular corneas contain trace quantities of VEGF, which is regarded as a powerful neurotrophic growth factor. Accordingly, prolonged use of anti-VEGF medications may result in neurotrophic keratopathy by decreasing corneal innervation (12).

2. Modified immunological responses: VEGF is thought to be a powerful chemo-attractant for inflammatory cells, which results in a robust corneal inflammatory response. Anti-VEGF medications may make it harder to mount a successful defense (12).

3. Issues with wound healing: By neutralizing VEGF-C and -D and preserving the corneal angiogenic privilege, VEGFR3 expression helps VEGF play a significant role in wound healing of the corneal epithelium, even in the avascular cornea. Additionally, it may impact epithelial proliferation and aid in the recruitment of inflammatory cells, particularly macrophages, which may hinder the repair of corneal stromal wounds (13).

3. NSAIDs, or nonsteroidal anti-inflammatory medications

The possible use of NSAIDs in the treatment of corneal neovascularization has been investigated. Cyclooxygenase (COX), a protein involved in prostaglandin synthesis, is inhibited by NSAIDs.NSAIDs may inhibit the creation

of new blood vessels via having antiangiogenic effects. However, compared to other treatments, the data supporting the effectiveness of NSAIDs in treating corneal neovascularization is weaker. The primary purpose of NSAIDs is to prevent inflammation, which can result in corneal neovascularization. Instead of being a primary treatment for corneal neovascularization, NSAIDs ought to be viewed as an adjuvant (14).

4-Treating immunosuppression:

The effects of the immunosuppressive medication cyclosporine on angiogenesis have been investigated in a number of situations, most notably those involving transplantation and the immune system. Cyclosporine and angiogenesis have a complicated relationship; depending on the circumstances and cell types, the medication may have proangiogenic or antiangiogenic effects. A concentration of 0.1% is typically used for cyclosporine A. When the corneal disease process is severe, prescription drops are sometimes made at a greater concentration of 0.5–2%. Proinflammatory cytokines, such as IL-2 [T-cell growth factor (TCGF)], are inhibited by cyclosporine A. Lymphocytes in the G0 or G1 phase of the cell cycle are also selectively and reversibly inhibited by cyclosporine A. T cells passively absorb cyclosporine A when it is administered into the conjunctival sac, infiltrating the cornea and conjunctiva and preventing the release of proinflammatory cytokines like IL-2. Accordingly, cyclosporine A is an immunosuppressive medication that prevents the immune system's reaction, especially the activation of T lymphocytes (15).

5. Antisense Oligonucleotides, the substrate of the anti-insulin receptorOne important regulator of inflammation-induced angiogenesis has been shown to be anti-insulin receptor substrate (IRS-1). IRS-1 signaling was significantly decreased by an antisense oligonucleotide, and progressive CN was successfully and well-toleratedly stopped by anti-IRS-1 eye drops (Aganirsen) when treated twice daily.According to Cursiefen et al. (16), anti-IRS-1 treatment methods could be regarded as a safe and efficient topical strategy to target the expanding corneal angiogenesis.

B. The Angioocclusive/Angioregressive method

Angioregressive treatments

These entail the regression of pathologic ocular blood vessels that have already developed. Although removing angiogenic factors like VEGF can cause the regression of newly created blood vessels, older and mature vessels with pericyte coverings do not react to these removals. Regression of mature arteries is a complex process that typically requires anti-VEGF treatments in addition to vascular endothelial TIE2 receptor antagonists (Angiopoetin 2) (Ang-2). Endothelial cells, smooth muscle cells, and pericyte contact are lost as a result of the Ang-2/TIE2 interaction. In 2025, Kuribayashi H. et al. (17).

Angioocclusive methods

In high-risk vascularized corneas, angioocclusive techniques can assist avoid intraoperative bleeding during keratoplasty, control blood vessel leakage, and prepare the cornea for keratoplasty. It consists of

1. Fine-needle diathermy (FND) is a simple, rapid, economical, and dependable method. Corneal vessels can be cauterized directly or by inserting a suture needle into the vessel and cauterizing the tip of the needle. A number of corneal transplant rejection instances have been effectively reversed with the use of fine-needle diathermy (Fig. 1) (18).

The process: Using a microsurgical needle holder, a stainless steel 3/8 circle side cutting, single-armed needle with a 0.15 mm cross-sectional diameter and a 6.19 mm overall length is connected to a 10–0 monofilament black nylon suture. Parallel to and at the same depth as the blood vessel or vessels to be occluded, the needle is placed near the limbus. The needle tip can be inserted into the lumen of the blood vessel or vessels in comparatively bigger vessels. Unless the needle is accidentally removed prior to applying the diathermy probe, this is typically not linked to bleeding. The lowest power level on a unipolar diathermy unit (0.5–1 mA) is selected. Any unipolar diathermy unit that has this feature could be utilized. The patient's foot is strapped with the proper electrode, which is then attached to the apparatus. In the coagulating mode, the corneal needle and the diathermy probe are brought

into contact and kept there until the corneal stroma begins to mildly blanch, which normally takes a second or less. Every feeder vessel is handled separately. The needle is carried circumferentially for vessels that are dispersed along the graft–host junction and for very deep vessels that originate from an iris adhesion. The majority of the vessels are treated in a single session, but sometimes secondary (collateral) vessels that form after the initial session require a repeat operation. Treating the afferent arteries before blocking the efferents is always the goal. A single needle pass can treat both the afferent and efferent vessels at the same time if they are near to one another (19).

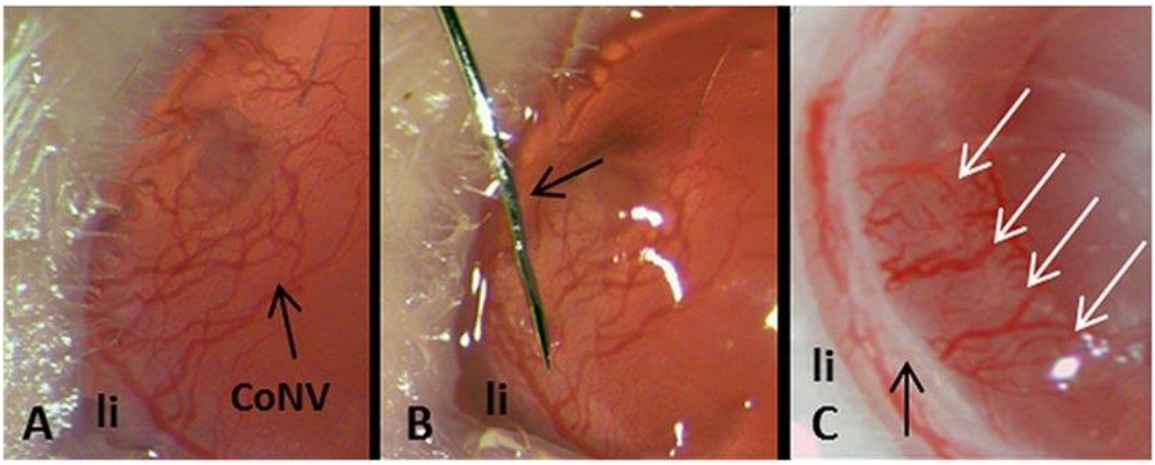

Fig. 1: Fine needle diathermy as a pretreatment in vascularized high-risk recipient eyes with pathological corneal neovascularization (CoNV; (A)). (B) Fine needle (arrow) was placed intrastromally and parallel to limbus (li). (C) After FND treatment, coagulated tissue (black arrow) was seen as a white band, separating corneal limbus (li) and coagulated vessels without erythrocyte flow (white arrows) **(18).**

Complications

1. Temporary corneal whitening: This type of whitening often goes away in 24 to 48 hours and affects the cornea close to the needle insertion site.

2. Hemorrhage: Bleeding may occur subconjunctivally, beneath the conjunctiva, or intrastromally, within the cornea. Usually, these go away in a few weeks.

3. Fewer frequent issues• Recurrence: Following treatment, neovascularization may occasionally recur. • Crystalline Deposits: When intracorneal hemorrhages stop, these deposits may develop in the stroma. • Corneal Perforation: Although uncommon, this dangerous consequence is possible. • Delayed Epithelialization: Following the operation, the cornea's surface may take longer to recover. • Greater Vascularization: FND's heat energy may encourage the production of substances that promote additional vascular development. • Damage to Deeper Structures: The limbus, or corneal border, and the corneal endothelium may be impacted by the application of thermal energy (20).

Second, Photocoagulation Induced by Laser

The vessel of interest is the selected focus of laser-induced photocoagulation, which causes heat-induced coagulation and vascular blockage (5). With varying degrees of success, argon, Nd:YAG, and yellow lasers have been employed for this purpose (Fig. 2) (21). Using a slit lamp delivery system without contact lenses, a frequency-doubled Nd-YAG laser (532 nm) is delivered with laser settings of 50–100 microns spot size, 100 ms exposure duration, and 250–550 mW (titrated) power. Up to the end point, the laser power is gradually increased in increments of 50 mW, starting with a minimum of 250 mW. End points are defined as the appearance of box-carring within the lasered vessel or the stoppage of blood flow. Corneal endothelial damage, corneal thinning, intraocular hemorrhage, pupillary displacement, iris atrophy, and corneal suture lysis following corneal transplantation are among the rare side effects linked to laser-induced photocoagulation.

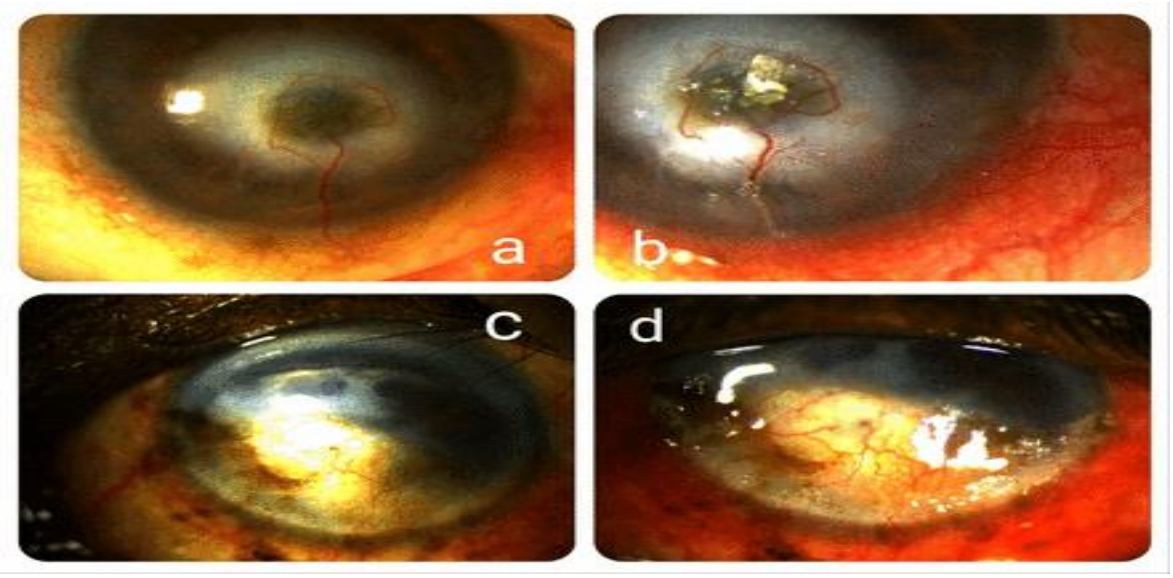

Fig. 2: The feeder vessel (a) can be lasered along its length for a minimum of 2 mm from limbus (b). Multiple vessels of different calibre (c) can be lasered using patterned laser (d) **(21).**

Unfortunately, proangiogenic substances that encourage the establishment of collateral circulation might be released as a result of laser-induced tissue injury. Laser-induced photocoagulation must be utilized in conjunction with anti-angiogenesis-specific medical treatments (such as anti-VEGF medicines) to minimize collaterals in order to solve this issue (8).

3. Photodynamic treatment of the cortex (PDT)

According to Stevenson et al. (5), this procedure involves injecting a photosensitizing agent intravenously into corneal vessels, where it is exposed to a specific wavelength of light (typical laser settings at 689 nm light). This causes the production of cytotoxic singlet oxygen, which damages vascular endothelial cells and causes vessel thrombosis.

CN has been treated with photosensitizing chemicals, including dihematoporphyrin, fluorescein, and verteporfin. While dihematoporphyrin photosensitizing agents have been linked to both local and systemic adverse effects (22), PDT with verteporfin or fluorescein can enhance CN regression with little risk (Fig. 3) (23).

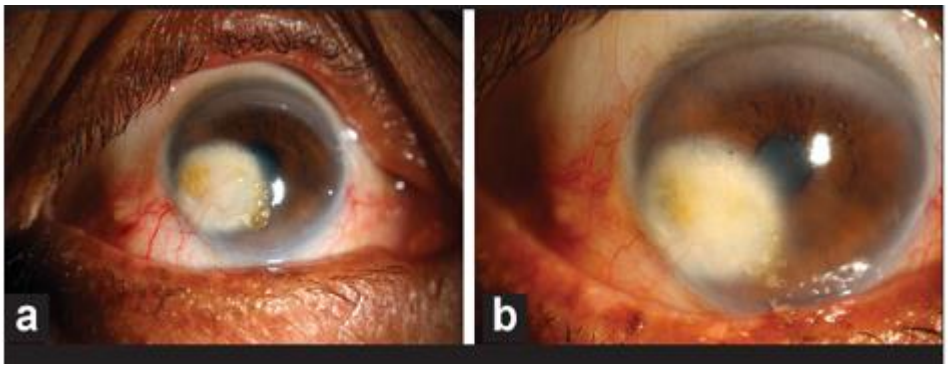

Fig. 3: (a) The baseline photograph shows deep corneal neovascularization with lipid exudation involving the visual axis. (b) 6 months after photodynamic therapy therapy with verteporfin. Note the significant reduction in the area of neovascularization and blood vessel caliber **(23).**

4- Mitomycin C intravascular chemoembolization(MICE):

In 2022, Dean P. Ouano introduced a revolutionary surgical procedure called mitomycin intravascular chemoembolization (MICE) to treat lipid keratopathy and visually significant corneal neovascularization.

Action mechanism:

The chemotherapeutic drug mitomycin C (MMC) is probably cytotoxic to vascular endothelial cells and has been used in transarterial chemoembolization (TACE) for the treatment of hepatocellular cancer (24). The reasoning behind this is that local therapy to reduce vascular endothelial cell proliferation may be delivered by selectively delivering MMC to aberrant corneal vessels. This would limit the blood vessel's endothelial monolayers' ability to heal. This gave rise to the innovative theory that corneal neovascularization might be effectively treated with MMC intravascular chemoembolization (MICE).

Method: A 33-gauge needle is connected to a 1.0 cc syringe that has been partially loaded with MMC (0.4 mg/mL). Just inside the limbus, the greatest bore corneal vessel is located. To cannulate the vascular, the needle is oriented at a 15-degree angle from the corneal surface. With sufficient retrograde hydrostatic force, a tiny amount of MMC (0.01 to 0.05 ml) is injected to fill the afferent and efferent channels. In any event, intravascular injections of mitomycin are limited to a total volume of 0.05 ml. To eliminate any remaining ocular surface MMC, the ocular surface is carefully irrigated with a balanced salt solution (Fig. 4) (25).

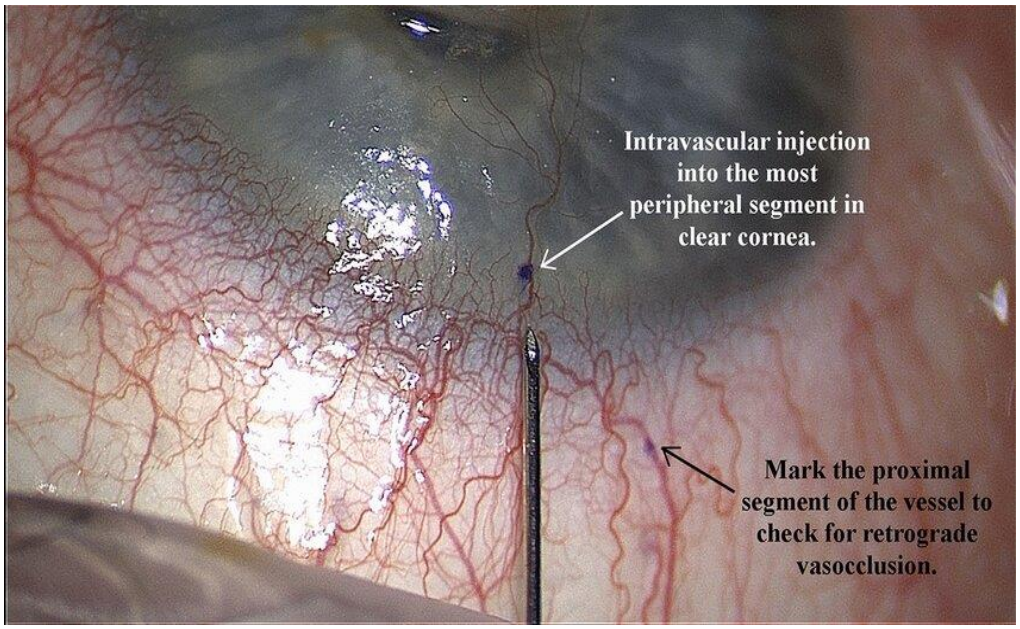

Fig. 4: The largest bore corneal vessel just inside the limbus was identified (white arrow). The needle was angled at approximately 15 degrees from the corneal surface to cannulate the vessel. A small volume of MMC (0.01 to 0.05 ml) was injected with enough retrograde hydrostatic force to fill both the efferent and afferent vessels (black arrow) **(25).**

Role of ocular surface reconstruction in management of CN

The last resort for individuals with refractory CN, superficial keratectomy, and corneal transplantation is ocular surface reconstruction.

A-Amniotic Membrane Transplantation: The amniotic membrane is made up of a non-vascularized, hypocellular matrix, a thick basement membrane, and a monolayer of epithelium.The amniotic membrane graft preparation is shown in Fig. 5 (26).

TIMP2 proteins, which are released by the amniotic membrane, dramatically lower bFGF and prevent fibroblasts from differentiating into myofibroblasts. Suturing the amniotic membrane, which has anti-inflammatory and antiangiogenic properties, may be part of the treatment for CN. The proliferation of corneal epithelial cells is best supported by the amniotic membrane. The amniotic membrane's laminin, fibronectin, type IV, V, and VII collagen, as well as integrins 4 and 6, promote corneal epithelial cell differentiation and hyperplasia, improve their adherence to the basement membrane, and regenerate limbal stem cells. Amniotic

basement membranes are nearly perfect for reconstructing the ocular surface because of their composition, which is comparable to that of the conjunctiva and cornea. The development of fibrovascular tissue and neovascularization may be inhibited by the amniotic membrane. According to these findings, amniotic membrane transplantation may help treat severe alkaline eye burns in their early stages by preventing corneal neovascularization (27, 28).

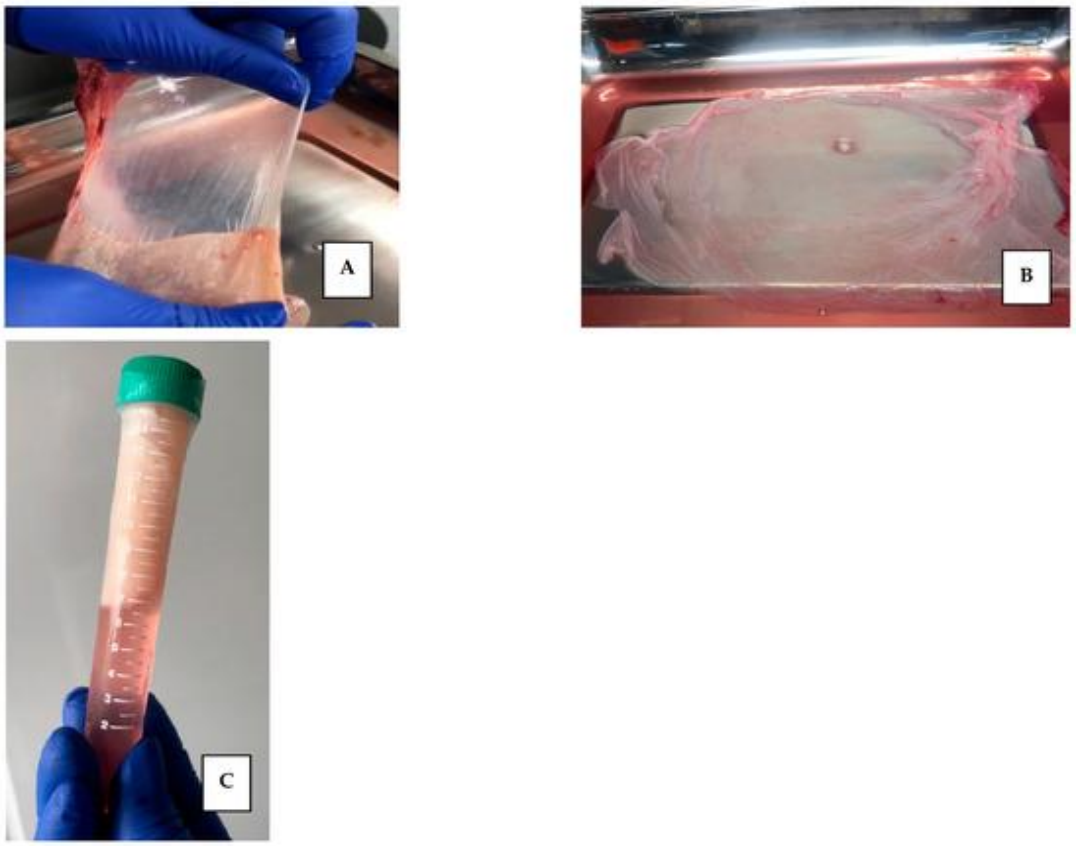

Fig. 5: (A) Separation of the amniotic membrane from the chorionic membrane.(B)Complete hAM before fractionation.(C) hAM on nitrocellulose paper preserved in DMEM and glycerol solution **(26).**

B-Corneal Limbal Stem Cell Transplantation:

Patients with limbal epithelial stem cell deficit (LSCD, LESCD) may benefit from limb stem cell transplantation (Fig. 6) (29). Numerous hereditary or acquired disorders, including Stevens-Johnson syndrome, contact lens keratopathy, and chemical or thermal damage to the cornea, can cause LSCD. These disorders result in corneal opacity, inflammation, neovascularization, and ultimately scarring.

The sources of limbal stem cell transplantation include cultured autologous or allogeneic grafts, in which the graft is taken and expanded from LSC samples and the stem cells are taken from the patient's or donor's eye; direct autologous transplants, in which the graft is taken from the patient's healthy eye; and direct allogeneic transplants, in which the graft is taken from a healthy donor (30).

Depending on the severity of LSCD, patients must make a difficult decision regarding stem cell transplantation. Allogeneic transplantation is used in situations where autologous transplantation is not feasible, such as severe bilateral LSCD. Despite receiving rigorous immunosuppressive treatment, the prognosis for allografts is significantly worse.

SLET (simple limbal epithelial transplantation), CLAU (conjunctival–limbal autografting), CLET (ex vivo cultivated limbal epithelial transplantation), and KLAL (keratolimbal allograft) are the surgical techniques currently employed to treat LSCD (31).

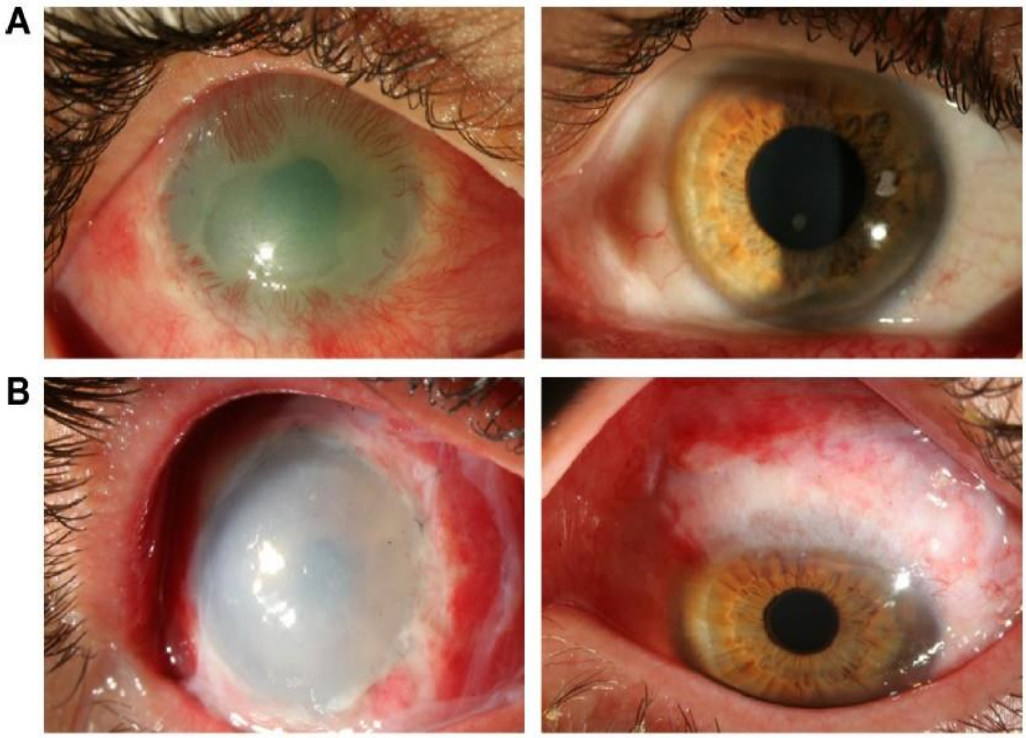

Fig. 6: (A) Patient with limbal stem cell deficiency after chemical burn with neovascularization and scarring(left) and donor eye with healthy stem cell niche (right). **(B)** Slit-lamp photograph after autologous stem cell transplant in affected (left) and donor eye (right) **(29).**

C-Superficial Keratectomy:

The surface layers of the cornea, such as the epithelium, Bowman's membrane, and occasionally the superficial corneal stroma layers, are surgically removed during a superficial keratectomy. Neovascularization is one of the corneal disorders that can be treated by superficial keratectomy. The goal of superficial keratectomy is to remove aberrant blood vessels that cause corneal scarring, inflammation, decreased visual acuity, and even vision loss by reducing corneal translucency and impairing corneal function. Mitomycin C (0.02%) can be administered intraoperatively to improve surgical outcomes by reducing postoperative ocular haze or amniotic membrane transplantation. By removing the underlying cause—abnormal blood vessels—superficial keratectomy promotes the cornea's natural healing processes. Following the surgery, the surrounding healthy tissue regenerates and the cornea starts to mend (32).

D-Corneal Transplantation: When opacity and neovascularization have severely compromised visual acuity, corneal transplantation is carried out. Anti-VEGF solution is injected subconjunctivally into patients with corneal neovascularization to prepare them for corneal transplantation. After corneal transplantation, antiangiogenic therapy is also given to avoid graft rejection (Fig. 7) (33). Patients with refractory central corneal neovascularization (Fig. 8) who experience repeated graft failure or rejection may benefit most from keratoprosthesis insertion (34).

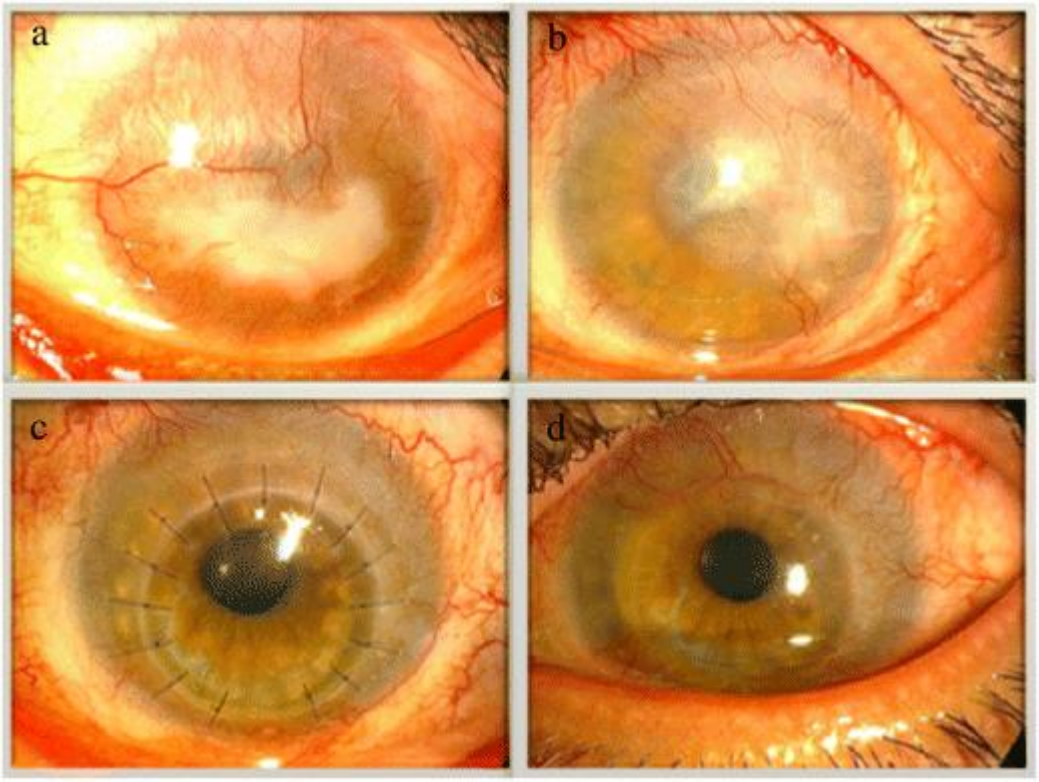

Fig. 7: Penetrating keratoplasty in a patient after cultivated limbal epithelial transplantation (CLET). a Before CLET. b 6 months after CLET. c 3 months after PKP. d A year and a half after PKP **(33).**

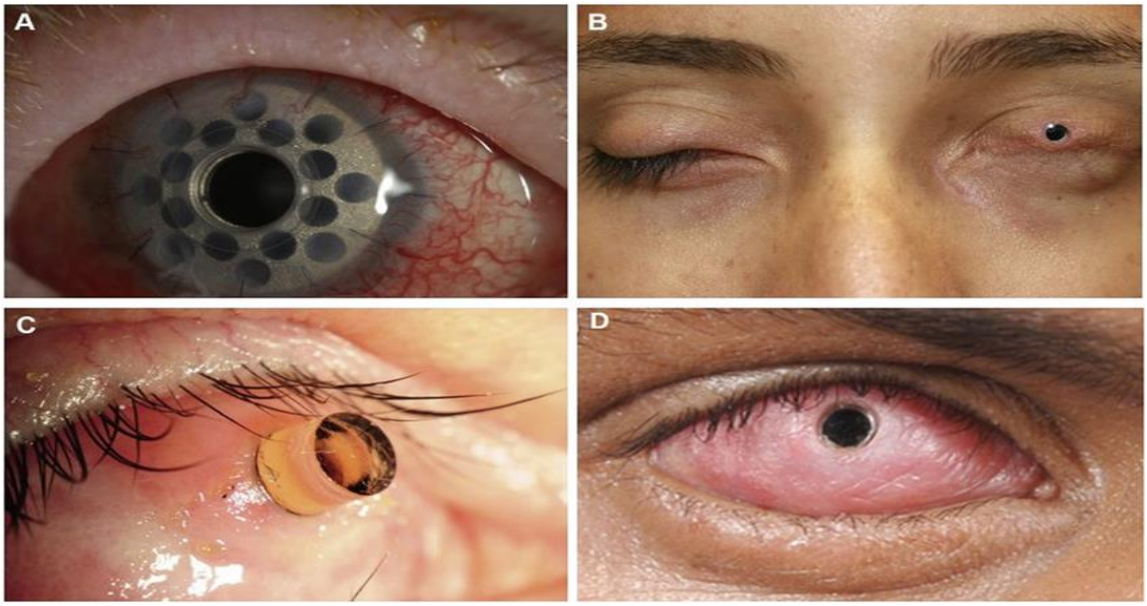

Fig. 8: Keratoprosthesis implantation (A) Boston keratoprosthesis type I. (B) Boston keratoprosthesis type II. (C) Osteo-odonto-keratoprosthesis. (D) LVP Keratoprosthesis **(34).**

Other medical therapies to treat CN:

1-TIMPs

By attaching to active MMPs and preventing their enzymatic activity, TIMPs are endogenous inhibitors that cells make to control MMP activity. Corneal neovascularization in inflammatory situations can be prevented by

inhibiting enzymes that jeopardize the structural integrity of the cornea. There are four known TIMPs (TIMP1–4), and while their structures are similar, their expression profiles and levels of affinity vary. Growth factors and cytokines control TIMP activity. All known human ECM proteases are inhibited by TIMP2-4. Doxycycline is a non-selective metalloproteinase inhibitor belonging to the tetracycline category of antibiotics. Doxycycline chelates calcium and zinc ions to prevent metalloproteinase action. On the first day of treatment for corneal neovascularization, 100 mg of oral doxycycline is taken twice daily. Thereafter, a maintenance dose of 100 mg is taken once daily. Neovascularization is inhibited when topical corticosteroids and oral doxycycline are combined (35).

2-Inhibitors of Tyrosine Kinase

VEGFR-2, PDGFR-β, FGFR-1, and EGFR are the four RTK receptors implicated in angiogenesis that are specifically and potently inhibited by sunitinib, a multitargeted RTK inhibitor. Sunitinib effectively decreases angiogenesis when given orally to animals with inflammation-induced ocular neovascularization, most likely by inhibiting the VEGFA/VEGFR-2 pathway (36).

Significant decreases in VEGFR-2 levels and neovascularization have also been linked to topical application of sunitinib at a concentration of 0.5 mg/mL. Because sunitinib inhibits the VEGF and PDGF pathways, it is three times more efficacious than bevacizumab when applied topically to treat corneal neovascularization. Additionally, local administration produced superior benefits than subconjunctival injection (37).

3. Inhibitors of Galectin-3

Anti-VEGF medications work well as treatments. Nevertheless, they have little effect on mature neovascularization, which includes arteries coated with pericytes. Galectin-3 inhibitors show promise since they influence the cornea's fibrotic processes and slow the progression of corneal neovascularization (38).

4. PEDF, or Pigment Epithelium-Derived Factor

Through the inhibition of endothelial cell migration to neovascularization regions and the concurrent induction of death, PEDF suppresses angiogenesis via VEGF, bFGF, and IL-8 (CXCL8). Exogenous PEDF may decrease ocular neovascularization and prevent the formation of new blood vessels (39, 40).

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