Advancements in Neovascular Ophthalmopathy: Therapeutic Strategies and Future Prospects

Miaomiao Zhang¹, Xinyue Lu¹, Ge Li¹, Shixin Zhang¹, Jingbo Zhang¹, Xiaoge Fu¹, and Fengying Sun¹

¹Affiliation not available

October 19, 2023

Abstract

Abnormal ocular angiogenesis is a key factor in the development of many blinding ocular diseases, including wet age-related macular degeneration (wAMD), diabetic macular oedema (DME), pathologic myopia with choroidal neovascularization (PM-CNV), and neovascular glaucoma (NVG). The development of anti-neovascular drugs and ocular drug delivery systems (DDS) offers more possibilities for the treatment of neovascular eye diseases. In addition to anti-vascular endothelial growth factor (anti-VEGF) agents, the discovery of other anti-angiogenic targets, such as somatostatin, endostatin and pigment epithelium-derived factor (PEDF), has been a boon to patients with poor anti-VEGF efficacy and led to a reduction in the adverse effects of long-term VEGF inhibition. Gene therapy is currently a very promising approach for the treatment of neovascular ophthalmopathy. The rapid development of gene therapy and the potential for viral vector-mediated gene delivery to achieve sustained expression of anti-vascular substances at the lesion site will mitigate the risks associated with frequent intraocular injections for patients. This review provides an overview of several neovascular ophthalmopathies, discusses the use of anti-vascular therapeutic agents and common DDS, and summarizes treatment strategies and future perspectives for neovascular ophthalmopathy.

Advancements in Neovascular Ophthalmopathy: Therapeutic Strategies and Future Prospects

Highlights

* Neovascular ophthalmopathy is caused by an imbalance between proangiogenic and antiangiogenic processes in the body
* Vascular growth factor is a key factor in neovascular ophthalmopathy
* Gene therapy may be more effective than traditional drug therapy in treating neovascular ophthalmopathy
* Viral delivery system promises longer-lasting treatment for neovascular ophthalmopathy

Abstract

Abnormal ocular angiogenesis is a key factor in the development of many blinding ocular diseases, including wet age-related macular degeneration (wAMD), diabetic macular oedema (DME), pathologic myopia with choroidal neovascularization (PM-CNV), and neovascular glaucoma (NVG). The development of anti-neovascular drugs and ocular drug delivery systems (DDS) offers more possibilities for the treatment of neovascular eye diseases. In addition to anti-vascular endothelial growth factor (anti-VEGF) agents, the discovery of other anti-angiogenic targets, such as somatostatin, endostatin and pigment epithelium-derived factor (PEDF), has been a boon to patients with poor anti-VEGF efficacy and led to a reduction in the adverse effects of long-term VEGF inhibition. Gene therapy is currently a very promising approach for the treatment of neovascular ophthalmopathy. The rapid development of gene therapy and the potential for viral
vector-mediated gene delivery to achieve sustained expression of anti-vascular substances at the lesion site will mitigate the risks associated with frequent intraocular injections for patients. This review provides an overview of several neovascular ophthalmopathies, discusses the use of anti-vascular therapeutic agents and common DDS, and summarizes treatment strategies and future perspectives for neovascular ophthalmopathy.

Graphical abstract

Keywords
Neovascular Ophthalmopathy, VEGF, anti-angiogenic drugs, gene therapy, delivery system

Introduction

Angiogenesis and neovascularization are two distinct concepts. Angiogenesis refers to the formation of new blood vessels on pre-existing ones, while neovascularization involves the creation of entirely new blood vessels[1]. Angiogenesis is a process that builds upon existing blood vessels, and it is triggered by factors such as VEGF and other cell growth factors. These factors promote the proliferation and migration of endothelial cells, leading to the organized formation of blood vessels[2, 3]. Angiogenesis is closely associated with the regulation of growth factors and cell signalling[4]. In general, angiogenesis does not occur in adulthood unless it is induced by pathological conditions such as ischaemia[5].

Neangiogenesis occurs continuously throughout the human body and plays a crucial role in various physiological processes. It is involved in the organ development during embryogenesis and contributes to the repair of damaged tissues in adults[6]. The formation and growth of blood vessels result from intricate regulatory mechanisms. However, when these regulatory signals become aberrant, it can lead to abnormal angiogenesis, thereby disrupting the organism’s homeostasis. Excessive angiogenesis, for instance, can give rise to neovascular ophthalmopathies, while uncontrolled angiogenesis is believed to be associated with cancer[7-9]. Conversely, insufficient or excessive angiogenesis can have detrimental consequences, including stroke, myocardial infarction, and neurodegenerative disorders[10-12].

Ocular neovascularization can manifest in various structures of the eye, including the retina, choroid, iris and cornea[13]. Uncontrolled neovascularization in the eye can lead to visual impairment, macular scarring, macular edema, glaucoma, and even the risk of blindness[14]. Persistent pathological neovascularization can lead to diseases such as wAMD, DME, retinopathy of prematurity (ROP), and corneal neovascularization (CRNV), and of which can result in visual impairment for affected individuals (Fig.1)[15, 16].
Pathogenesis of ocular neovascularization

Ocular neovascularization represents an abnormal angiogenic process that can lead to various ocular disorders, often resulting in significant vision impairment or loss for patients. While the exact etiology of ocular neovascularization remains incompletely understood, it is believed to be associated with factors such as ocular inflammation, contact lens use, trauma, and viral infections\cite{17-19}. The pathogenesis of ocular neovascularization is a multifaceted process characterized by the activation, proliferation, and migration of endothelial cells (ECs), vasodilatation, heightened vascular permeability, increased inflammation, and degradation of the surrounding extracellular matrix\cite{20}. Ocular neovascularization is inherently fragile due to its lack of structural integrity, notably the absence of a basement membrane and pericytes, rendering it susceptible to leakage. Such fluid leakage and subsequent fibrosis can inflict damage upon ocular tissues, ultimately jeopardizing vision and precipitating severe eye diseases\cite{16, 21}.

Neovascular Eye Disease

3.1 wAMD

Age-related macular degeneration (AMD) stands as the foremost cause of irreversible vision loss among individuals aged 60 and above. Early AMD exhibits a higher prevalence in Europeans compared to Asians, affecting hundreds of thousands of individuals worldwide\cite{22}. The onset of AMD is multifactorial, closely intertwined with factors such as aging, genetics, and environmental risk factors like obesity, hypertension\cite{23-25}. AMD is categorically divided into two primary types: dry macular degeneration and wet macular degeneration, both stemming from structural and functional deterioration of the macular region of the retina\cite{26}. The macula, located between the retina and the iris, is a critical area in AMD diagnosis. The presence of yellow deposits, known as drusen, in the macula is considered an early sign of dry AMD. Left untreated, drusen multiply over time, exacerbating the condition and eventually culminating in vision loss\cite{27-29}. Dry AMD often progresses to wAMD in approximately 10-20% of patients as the disease advances to a later stage\cite{30}. About 15% of AMD patients ultimately develop wAMD. Wet macular degeneration is characterised by pathological neovascularization within the macula, primarily in the form of choroidal neovascularization (CNV), which
features thin features walls that are prone to fluid leakage (plasma)\textsuperscript{31-33}. Persistent abnormal neovascularization and subsequent leakage can result in fluid accumulation, haemorrhage, or fibrosis, rapidly leading to central vision loss (Fig. 2)\textsuperscript{25}. Current treatment strategies for wAMD predominantly rely on intravitreal injections of anti-VEGF drugs. These drugs effectively control neovascularization and decelerate the progression of vision loss. However, the therapeutic regimen involving frequent intravitreal injections remains burdensome. Patients would benefit from therapies with reduced dosing frequency and a lower number of intraocular injections \textsuperscript{34}.

Fig. 2. Pathological course of wAMD. wAMD is characterized by choroidal neovascularization that sprouts and grows, culminating in neovascular fluid leakage, macular oedema, and vision loss.

3.2 DME

DME is a complication that occurs in individuals with diabetes mellitus and stands as the primary cause of vision impairment among those with diabetic retinopathy (DR), especially among individuals with type II diabetes mellitus\textsuperscript{35}. Risk factors for DME include hyperglycemia, hyperlipidemia, hypertension, inflammation, and oxidative stress, all of which become increasingly prevalent as the diabetic population continues to grow\textsuperscript{36}.

DME manifests as a consequence of diabetes-induced disruption of the blood-retinal barrier (BRB) and subsequent fluid leakage, resulting in macular edema. This condition is often accompanied by the deposition of exudates in the central retina\textsuperscript{37-42}. Two forms of DME exist: focal and diffuse macular edema. Focal macular edema is caused by localized leakage from retinal microaneurysms and dilated capillaries, while diffuse macular edema results from the widespread leakage of dilated retinal capillaries throughout the posterior segment\textsuperscript{43-45}. Upregulation of VEGF has been associated with DME, and as a result, anti-VEGF drugs have become a common treatment approach. A significant proportion of DME patients have reported favorable responses to anti-VEGF drugs for at least two years\textsuperscript{46}. Despite the effectiveness of anti-VEGF drugs in managing DME, some patients still experience vision loss, prompting the exploration of alternative therapies for DME treatment\textsuperscript{47}.

3.3 PM-CNV

A study revealed that over 20% of the global population is currently myopic, with nearly 3% classified as highly myopic. It is projected that more than half of the world’s myopic population and nearly 10% of the highly myopic population will be affected by myopic by the year 2050\textsuperscript{48}. Highly myopic eyes are more susceptible to pathological changes, often progressing to pathological myopia\textsuperscript{49, 50}. Pathological myopia associated with various complications, and CNV is one of them\textsuperscript{51, 52}. In the context of pathological myopia with CNV, the primary locus of concern is the peripapillary macula. This condition is characterized by
choroidal neovascularization, fluid leakage, choroidal atrophy, and ultimately results in severe vision loss [53, 54]. Current treatment modalities for the disease include thermal laser photoacoagulation and photodynamic therapy employing vitexoparin. However, these treatments primarily aim to prevent further vision loss and do not effectively impede disease progression [55].

3.4 NVG

Glaucoma ranks as the second leading cause of blindness worldwide, with women disproportionately affected, according to research [56]. NVG represents a secondary form of glaucoma characterized by persistent eye pain and blindness, making it a challenging condition to manage [57, 58]. NVG emerges as a consequence of retinal ischaemia, leading to the formation of new blood vessels in the iris and angle of the eye, accompanied by connective tissue growth. This vascular proliferation hinders the aqueous humor outflow and increased intraocular pressure (IOP), eventually resulting in glaucomatous optic neuropathy [59, 60]. Multiple factors can trigger NVG, with common culprits including diabetic retinopathy (PDR), ischaemic central retinal vein occlusion, and ocular ischaemia syndrome [61, 62]. Present treatments for NVG primarily focus on mitigating neovascularization and reducing IOP [63]. Studies have shown that treatments involving anti-VEGF agents and surgical interventions can effectively lower intraocular pressure in the short term. However, NVG remains a challenging condition to cure, and currently available interventions do not provide a definitive cure [64-66].

3.5 ROP

ROP is a proliferative vitreoretinopathy that predominantly affects preterm infants, standing as a prominent cause of childhood blindness on a global scale [67]. While mild ROP often resolves spontaneously, severe cases can lead to retinal detachment and permanent blindness [68]. ROP can be identified through the screening of preterm infants based on their birth weight and gestational age, and timely intervention can prevent blindness resulting from ROP [69-71]. The pathogenesis of ROP is linked to the incomplete development of the neuronal and vascular components of the retina in preterm infants. This lag in development triggers compensatory mechanisms that culminate in abnormal neovascularization. Several factors, such as the postnatal exposure of the retina to high oxygen concentrations in closed incubators, further elevate the risk of blindness associated with ROP [72, 73]. Disease progression in children afflicted with ROP is closely associated with the development of abnormal neovascularization. VEGF is a key driver of neovascularization. Consequently, the administration of anti-VEGF drugs has emerged as a promising strategy for controlling abnormal neovascularization in the retina. Studies have indicated that Ranibizumab may offer a safer and more effective alternative to traditional laser treatment for ROP. However, it is crucial to be attentive to the risk of periocular infections resulting from vitreous injections [68].

3.6 CRNV

CRNV represents a global condition that significantly affects a patient’s vision, leading to the clouding of the cornea and recurrent inflammatory cycles [74, 75]. The cornea is normally a clear, avascular, and Immune-privileged tissue [76, 77]. However, when the eye undergoes pathological damage due to infection, trauma, or inflammation, the cornea’s avascularity cannot be maintained. This disruption results in an imbalance between pro-angiogenic factors (e.g., VEGF) and anti-angiogenic factors. Pro-angiogenic factors take precedence, leading to the invasion of capillaries from the corneal limbal vascular plexus and the formation of neovascularization [78-80]. The secretion of pro-angiogenic factors promotes CRNV, which, in turn, causes corneal clouding and the deposition of lipids and proteins. This process triggers an inflammatory response in the eye [75, 81-83]. Treatment for CRNV often involves the use of anti-VEGF drugs. Recent studies have also explored the potential of protein kinase B (Akt) inhibitors as new therapies for the treatment of CRNV [84].

Ocular neovascularization drugs

4.1 VEGF-related drugs

VEGF serves as a pivotal regulator of angiogenesis, exerting its effects on a wide array of cells and tissues, notably endothelial cells [85]. In the pathogenesis of ocular diseases like exudative AMD, DME, NVG, and ROP, VEGF-induced neoangiogenesis, mediated by insulin-like growth factor-1 (IGF-1), plays a central
role\textsuperscript{[86]}. VEGF elicits several angiogenic responses, including endothelial cell proliferation, stimulation of cell migration, enhancement of vascular permeability, promotion of neovascularization, and participation in various physiological processes\textsuperscript{[87]}. Within the mammalian VEGF family, five members exist: VEGFA, VEGFB, VEGFC, VEGFD, and placental growth factor (PIGF). VEGFA holds particular significance due to its pivotal role in regulating in vivo angiogenesis\textsuperscript{[88-90]}. Overexpression of VEGFA is often observed in patients with neovascular ocular diseases, leading to heightened endothelial cell invasiveness, increased blood vessel formation, and fluid leakage within the eye, ultimately impairing vision\textsuperscript{[85]}. VEGF exerts its angiogenic effects through two primary tyrosine kinase receptors (RTKs), namely VEGFR-1 (which regulates VEGF receptor) and VEGFR-2 (which controls angiogenic activity). These receptors collectively influence angiogenesis in the organism\textsuperscript{[18, 91]}. Recognizing its critical role in in vivo angiogenesis, VEGF has emerged as a key target for the treatment of neovascular ocular diseases. Consequently, therapies targeting the VEGF signalling pathway are actively under development\textsuperscript{[92]}. Anti-VEGF drugs have been developed to inhibit neovascular diseases, spanning from cancer to neovascular eye diseases, and have yielded promising results. Studies have shown that patients with neovascular ocular diseases, treated with intravitreal injections of anti-VEGF drugs, experience significant vision improvement\textsuperscript{[93]}. These anti-VEGF drugs can be categorized into several types, including anti-VEGF antibodies, anti-VEGF aptamers, and kinase inhibitors, all of which effectively inhibit abnormal angiogenesis within the posterior segment of the eye.

4.1.1 Anti-VEGF antibodies

Anti-VEGF antibody drugs, notably bevacizumab and ranibizumab, have demonstrated significant efficacy in inhibiting VEGF-induced angiogenesis\textsuperscript{[94]}. Additionally, Abciximab and Compeximab have been used in the treatment of neovascular ocular diseases such as AMD, DME, and CNV, showing promising therapeutic outcomes\textsuperscript{[95]}. Bevacizumab is a VEGF-neutralizing medication originally employed in the treatment of metastatic colorectal cancer. It stands as the first FDA-approved anti-angiogenic therapy targeting VEGF\textsuperscript{[96-99]}. Both bevacizumab and ranibizumab are recombinant humanized monoclonal antibodies targeting VEGFA. They work by binding to VEGFA, thereby blocking its interaction with its receptor. This action inhibits endothelial cell activation and proliferation\textsuperscript{[100-102]}. It’s worth noting that while both bevacizumab and ranibizumab fall under the category of anti-VEGF antibodies, bevacizumab is a full-length anti-VEGF antibody, whereas ranibizumab is an antibody fragment targeting VEGF, making it smaller than the bevacizumab fragment. Both exhibit a dose-dependent inhibitory effect on endothelial cell proliferation\textsuperscript{[103]}. Abciximab and compeximab, on the other hand, are recombinant anti-VEGF fusion proteins, distinguishing them from the monoclonal antibodies mentioned above\textsuperscript{[104, 105]}. Abciximab, following bevacizumab, is another anti-VEGF antibody drug with a broader spectrum of action. It impedes the binding of not only VEGFA but also VEGFB and PIGF to their respective receptors by directly binding to them, achieving an anti-angiogenic effect\textsuperscript{[106, 107]}. Abciximab is frequently employed in the treatment of central retinal vein occlusion\textsuperscript{[108]} and DR\textsuperscript{[109]}. While the class of anti-VEGF antibody drugs remains effective in the treatment of ocular neovascularization, some patients may exhibit reduced responsiveness or even resistance, necessitating alternative classes of drugs for their treatment.

4.1.2 Anti-VEGF aptamers

In addition to the aforementioned anti-VEGF antibody therapies, another approach for treating neovascular eye diseases involves small molecule nucleic acid aptamers\textsuperscript{[110]}. Nucleic acid aptamers are short, single-stranded DNA or RNA molecules that achieve target binding by adopting intricate secondary and tertiary structures, thereby inhibiting the function of target proteins\textsuperscript{[111-113]}. Aptamers offer several advantages over antibody drugs, including their smaller size, flexible structure, and heightened specificity\textsuperscript{[114]}. Furthermore, the structural diversity and modifiability of aptamers\textsuperscript{[115]} grant them a wide range of potential targets\textsuperscript{[116-118]}. However, aptamers also have limitations in clinical application. Firstly, they are synthesized in vitro, necessitating validation of their in vivo efficacy\textsuperscript{[119]}. Secondly, their small size can lead to rapid renal clearance.
and shorter systemic retention. Thirdly, the nucleic acid nature of aptamers renders them vulnerable to degradation by endogenous nucleases and less stable within the body \[120\]. Addressing these challenges in clinical application would expedite the development of aptamers.

The VEGFA family comprises multiple isoforms, including VEGF\(_{121}\), VEGF\(_{165}\), VEGF\(_{189}\) and VEGF\(_{206}\). These isoforms are often distinguished by their heparin-binding capabilities\[121, 122\]. Among them, VEGF\(_{165}\) is the most abundant isoform in tissues, exhibiting greater quantity and activity in the human body. It plays a pivotal role in regulating neovascularization and serves as a key factor in ocular neovascularization\[88\]. Consequently, therapeutic strategies targeting VEGF\(_{165}\) have gained prominence. In 2004, the FDA approved the marketing of pegaptanib, a drug that selectively blocks VEGF\(_{165}\), for the treatment of neovascular eye diseases. Pegaptanib marked the first RNA aptamer drug approved for the treatment of neovascular AMD and DME. However, its performance has been less than satisfactory\[85, 123, 124\]. In a clinical trial comparing intravitreal pegaptanib to bevacizumab and ranibizumab in patients with ocular neovascularization, pegaptanib was found to be less effective in improving vision than the other two agents\[125\]. Pegaptanib exclusively targets the 165 subtype of VEGFA, whereas ranibizumab acts on the entire VEGFA target. Due to its limited efficacy, pegaptanib was withdrawn from the market\[104\].

Indeed, in practical applications, the search for aptamers that are well-suited to specific targets within databases can be a significant challenge. The development of aptamer drugs is indeed hindered by the difficulties associated with aptamer discovery and optimization. However, ongoing research and advancements in aptamer technology continue to address these challenges, offering hope for the development of effective aptamer-based therapies in the future.

4.1.3 Enzyme inhibitors

As previously mentioned, VEGF exerts its angiogenic effects through RTKs. Small molecule tyrosine kinase inhibitors have been developed to interfere with the VEGFR signaling pathway and impact neoangiogenesis. Among the antiangiogenic drugs in the enzyme inhibitor class are the multikinase inhibitors sorafenib\[126, 127\], pazopanib\[128, 129\], and sunitinib\[130\]. Sorafenib, for instance, has shown promise in inhibiting CRNV when administered orally to rats, with dose-dependent efficacy observed. It was found to inhibit extracellular signal-regulated kinase phosphorylation in the rat cornea \[131, 132\]. Oral sorafenib has also demonstrated the ability to reduce macular edema and stabilize vision\[133\]. However, systemic toxicity associated with oral sorafenib is not negligible, and its bioavailability is limited. Research into new delivery systems is necessary to mitigate drug toxicity. In an effort to minimize the risks associated with intravitreal injections, researchers explored novel nanostructured microemulsion systems for delivering sorafenib to the posterior segment of the eye. In 2021, they found that the microemulsion system containing 0.3% sorafenib effectively inhibited 54% of laser-induced neovascularisation in mouse eyes with CNV. It also reduced the expression of proinflammatory factors in a model of retinal disease, indicating its effectiveness in delivering the drug to the posterior segment of the eye\[134\]. Subsequently, it was demonstrated that nanolipid carriers loaded with sorafenib were biocompatible for topical ocular delivery and were as effective as dexamethasone in inhibiting corneal neovascularisation in mice \[135\].

Pazopanib, on the other hand, exhibited significant interspecies differences in ocular infusion in animal models of CNV. Concentrations in the posterior segment of the monkey’s eye were much lower than in the rat’s eye, making effective delivery to the monkey’s eye challenging\[136\]. In patients with neovascular AMD, pazopanib drops were reported to cause painful ocular irritation and were found to be ineffective\[137\]. Sunitinib showed better results compared to pazopanib. In 2021, researchers showed that sunitinib could be formulated into microcrystals through ion complexation. Subconjunctival injection of these microcrystals was effective in rats with CNV\[138\]. Additionally, some researchers developed liposomes loaded with sunitinib, which were found to inhibit neovascularisation in a mouse model of laser-induced CNV, indicating the potential of this liposomal formulation as a drug delivery system\[139\].

Efforts to investigate more efficient delivery systems for kinase inhibitors of anti-VEGF drugs are essential to reduce the systemic toxicity associated with oral administration and minimize eye damage caused by frequent
intravitreal injections. The development of new delivery systems is urgently needed for the treatment of neovascular eye diseases.

4.2 Other inhibitors

4.2.1 Somatostatin

Ocular neovascularization involves a delicate balance of inhibitory and growth factors. Somatostatin, a growth suppressor, plays a role in angiogenesis by inhibiting the growth hormone-insulin-like growth factor axis and directly suppressing the proliferation of human retinal endothelial cells[140]. Somatostatin is a tetrapeptide originally isolated from the hypothalamus of sheep and known to inhibit pituitary growth hormone secretion[141]. Two biologically active forms of somatostatin exist, SS-14 and SS-28, with differential expression in the retinas of various species[142]. Somatostatin is abundant in vitreous fluid and contributes to retinal homeostasis [143]. In experiments, SS-28 was found to be threefold higher than SS-14 in subjects with PDR and fivefold higher in non-PDR subjects, suggesting that SS-28 is the predominant active form of somatostatin in vitreous fluid [144]. Somatostatin acts as a regulatory peptide with antiproliferative effects by inhibiting hormone release through G protein-coupled receptors [145]. It plays a regulatory role in cell proliferation, immunity, vascular function, and neuronal function [146].

Studies have indicated that somatostatin and its analog, octreotide, can inhibit insulin-like growth factor-1 (IGF-1) receptor phosphorylation and reduce VEGF production in retinal pigment epithelial (RPE) cells, indicating their potential as therapeutic agents for treating neovascular eye diseases [86]. Analogous growth suppressors have also demonstrated their ability to inhibit neovascularization in animal models, such as the rat eye[147, 148]. To enhance the potential of growth suppressor analogs as therapeutic agents for neovascular eye diseases, researchers have explored innovative approaches. For instance, they combined octreotide with magnetic nanoparticles to create MNP-OCT. This formulation was found to maintain the efficacy of octreotide and even demonstrated improved effects at lower concentrations [149]. Other growth suppressor analogs, including lanreotide[150] and pareotide[151], have also exhibited anti-neovascular effects, further expanding the potential range of therapeutic options.

4.2.2 Endostatin

Endostatin is a 20 kDa protein fragment derived from the C-terminus of type XVIII collagen[152, 153]. It functions as an angiogenesis inhibitor, suppressing the invasion, migration, and proliferation of endothelial cells[154, 155]. Es is considered an endogenous anti-angiogenic factor that effectively inhibits VEGF expression and angiogenesis[156]. Studies have demonstrated that polyethylene glycolated recombinant human endothelial suppressor (M2ES) can inhibit the migration of human microvascular endothelial cells (HMEC) in vitro[157]. Furthermore, direct subretinal injection of M2ES in rats with CNV reduced vascular leakage[158]. Researchers have also developed novel proteins like Tat PDT-Es-RGD, which have shown excellent anti-angiogenic capabilities when applied as eye drops in a mouse model of oxygen-induced retinopathy[159]. In 2020, Ai Jing et al. introduced endothelin-lentivirus (ES-LV)-EPC gene therapy, which significantly inhibited retinal neovascularization in rats[160]. The demonstrated anti-angiogenic and vascular leakage-reducing effects of recombinant Es in animal models of CNV highlight its potential as a therapy for neovascular eye diseases.

4.2.3 Angiostatin

Angiostatin is a protein fragment resulting from the hydrolysis of fibrinogen and, like Es, serves as a naturally occurring endogenous inhibitor of angiogenesis[161, 162]. Angiostatin and related proteins are known to induce endothelial cell apoptosis while inhibiting endothelial cell activity and migration[163]. As early as 2003, studies found that vitreous injection of an HIV vector encoding angiostatin could inhibit retinal neovascularization in a mouse model of proliferative retinopathy, demonstrating the potential of angiostatin in treating neovascular eye diseases[164].

4.2.4 PEDF
PEDF belongs to the serine protease inhibitor superfamily and is an endogenous neurotrophic protein[165]. The PEDF gene is highly expressed in fetal and young RPE cells, localizing in both the nucleus and cytoskeletal structures of these cells. However, its expression decreases with age[166]. PEDF possesses anti-angiogenic and anti-tumor properties[167]. Previous studies on PEDF in rats with experimentally induced CNV by Nahoko Ogata et al. discovered that PEDF expression was initially higher in various cells during the early stages of photococagulation, then down-regulated, but still persisted in neovascular tissues. This suggests that PEDF may regulate the process of CNV formation[168]. Several studies have demonstrated the effectiveness of recombinant PEDF protein and PEDF cDNA in inhibiting neovascularization[169-171]. In recent years, Zhao Feng et al. have constructed PEDF-loaded polyethylene glycol nanoparticles that effectively inhibit the migration, proliferation, and tube formation of human umbilical vein endothelial cells (HUVECs) stimulated by high glucose. This opens up innovative therapeutic approaches for future neovascular eye diseases[172]. Additionally, PEDF-derived short synthetic peptides retain anti-angiogenic activity and may be more suitable as anti-angiogenic drugs than the full PEDF protein[173]. PEDF is currently used to treat neovascular eye diseases in various forms, including direct administration[174], nanoparticles (such as PLGA nanospheres and liposomes)[173, 175], and viral vectors[176, 177]. Each delivery method has its advantages and should be selected based on the specific treatment scenario. Further research is needed to explore better delivery modalities.

4.3 Other drugs

4.3.1 Non-steroid anti-inflammatory drug (NSAID)

NSAIDs are widely used for their antipyretic, anti-inflammatory and non-addictive properties[178]. NSAIDs exert their anti-inflammatory effects by inhibiting cyclooxygenase/prostaglandin-endoperoxide synthase (PGSH), which in turn inhibits the synthesis of prostaglandins associated with inflammation[179]. Inflammation is the body’s protective response to infection and tissue damage[180] and can be classified as acute or chronic based on the duration of the process[181-183]. Ocular inflammatory signaling pathways are very active, and the persistence of chronic inflammation in the eye can lead to neovascular eye diseases[184]. Therefore, anti-inflammatory drugs are commonly used in combination therapy for neovascular eye diseases[185]. Several NSAIDs have shown anti-inflammatory effects during inflammatory ocular neovascularization, such as loxoprofen sodium[186], nepafenac[187], indomethacin[188], and ketorolac[189]. Bromfenac sodium (BS) is a topical ophthalmic NSAID known for its good ocular penetration and is approved for use as an anti-inflammatory agent after ocular surgery[190]. Topical application of ocular NSAID can effectively avoid the adverse effects of gastrointestinal injury, renal injury, and hypersensitivity reactions associated with systemic drug administration[179, 191-193]. Better therapeutic outcomes are expected when NSAIDs are combined with anti-VEGF drugs for the treatment of neovascular eye diseases.

4.3.2 Glucocorticoid

Glucocorticoids are a class of steroid hormones and commonly used effective anti-inflammatory drugs that can inhibit VEGF activation and reduce the synthesis of proinflammatory and vascular leakage factors[194]. Glucocorticoids bind to cytoplasmic receptors, preventing their entry into the nucleus, which, in turn, inhibits the transcription of proinflammatory, vascular leakage, and angiogenic genes induced by these cytoplasmic receptors, thereby effectively restraining angiogenesis[195-197]. Common glucocorticoid drugs used to treat neovascular ocular diseases include triamcinolone[47, 198], dexamethasone[199, 200], fluocinolone acetonide[201], and flunisolide[202]. It was found that the triamcinolone group exhibited more significant reductions in central retinal thickness and notable decreases in interleukin-6 (IL-6), interferon gamma-induced protein 10 (IP-10), and VEGF levels compared to the bevacizumab group in patients with DME who received intravitreal triamcinolone injections. Conversely, the bevacizumab group displayed reduced VEGF levels only[203]. Research has demonstrated that dexamethasone implants, when combined with anti-VEGF treatment, lead to superior visual improvement and reductions in central retinal thickness compared to anti-VEGF treatment alone[204]. Consequently, the combination of GCs with anti-VEGF drugs may prove more effective than anti-VEGF monotherapy in the treatment of DME.
4.4 Gene therapy

Pathological ocular neovascularization often arises from an imbalance between proangiogenic and antiangiogenic factors\textsuperscript{[205, 206]}. Currently, the treatment of pathological ocular neovascularization heavily relies on antiangiogenic drugs. However, this monotherapy can merely decelerate disease progression and is incapable of delivering a complete cure. The short half-life of these drugs necessitates frequent intraocular injections, which can harm a patient’s vision. Furthermore, some patients develop drug resistance, leading to unsatisfactory treatment outcomes. In light of these challenges, gene therapy holds great potential for the treatment of pathological ocular neovascularization\textsuperscript{[207, 208]}. The eye offers unique advantages as a site for gene therapy: (1) The eye is physically separated from other organs, rendering it highly accessible and convenient for the delivery of therapeutic genes\textsuperscript{[208, 209]}; (2) The blood-eye barrier confers relative immune privilege to the eye, helping to prevent the escape of therapeutic genes into the systemic circulation to some extent\textsuperscript{[210]}; (3) Target cells in the retina are often highly differentiated cells that do not readily divide. Consequently, gene therapy can achieve more sustained effects and reduce the damage to vision resulting from frequent injections\textsuperscript{[211]}. Gene therapy in the context of ocular neovascularization presents exciting opportunities for the development of novel treatment modalities.

RNA-targeted therapy is a common gene therapy approach employed in ocular treatments. Small interfering RNAs (siRNAs) designed to target VEGFR can be efficiently delivered using nanoparticles, hydrogels, and other vehicles, effectively inhibiting VEGF mRNA and demonstrating promise in the treatment of neovascular eye diseases. Adenoviruses (AdVs) and lentiviruses (rLVs) have also been harnessed for delivering siRNAs\textsuperscript{[212]}. As far back as 2005, research indicated that subconjunctival injection of liposome-mediated brain-specific angiogenesis inhibitor 1 gene could significantly reduce experimental CRNV in rabbit eyes\textsuperscript{[213]}. In recent years, researchers have employed rLVs to deliver Cas9 mRNA and guide RNA targeting vascular VEGFA (Vegfa) to treat mouse models of wAMD. This approach effectively knocked out 44% of Vegfa in retinal pigment epithelium and reduced the area of CNV by 63%\textsuperscript{[214]}. Adeno-associated virus-mediated CRISPR/Cas9 systems with paired guide RNAs led to a 33% Vegfa gene disruption and approximately 30% reduction in CNV lesion size\textsuperscript{[215]}. Yin et al. also demonstrated that subretinal injection of AAV delivering CRISPR targeting Vegfa could inhibit neovascularization in a laser-induced CNV mouse model\textsuperscript{[216]}. Recombinant AAVs (rAAV1-pICAM2-SpCas9 and rAAV1-SpGuide) developed by Wu Wenyi et al. significantly reduced pathological retinal neovascularization in a mouse model of oxygen-induced retinopathy\textsuperscript{[217]}. In the realm of gene therapy for neovascular eye diseases, strategies encompass bolstering endogenous antiangiogenic factors such as PEDF, endostatin, and angiostatin\textsuperscript{[218]}, or utilizing CRISPR gene-editing systems to knock out various components in angiogenic pathways, such as VEGFR and HIF-1\textsubscript{α}\textsuperscript{[219-221]}. While gene therapy offers many advantages, practical applications still face numerous challenges. Viral vector delivery may induce inflammation due to partial viral leakage, and there is a risk of off-target effects. Therefore, further experiments are required to validate the reliability of gene therapy methods.

**DDS of ocular neovascularization**

The development of DDS has significantly improved the therapeutic effectiveness of drugs\textsuperscript{[245]}, particularly in ocular treatments where the blood-eye barrier poses challenges. DDS offers a more efficient approach to ocular therapy (Figure 1), effectively addressing issues like poor compliance, limited drug absorption, low bioavailability, and inadequate targeting in the treatment of ocular neovascularization\textsuperscript{[246]}. DDS enables precise control of drug concentrations at the treatment site, enhances targeting specificity, and can regulate drug release rates, thus increasing efficacy and safety\textsuperscript{[247]}. Common delivery systems for ocular neovascular drugs encompass both viral vectors and non-viral nanocarriers, such as liposomes, polymer nanoparticles (PNP), and gold nanoparticles (AuNPs), among others (Fig. 3)\textsuperscript{[248]}. These delivery systems offer substantial potential for improving ocular treatment and will be elaborated upon below.
AdV

AdVs are double-stranded DNA viruses$^{[249]}$. Replication-defective AdV vectors possess several advantages, including their ample capacity for genetic material, high expression levels, and relative ease of production. However, one of the primary drawbacks of AdV vectors is that high doses in practical applications can lead to a shortened duration of gene expression$^{[250]}$. Early research by Cashman et al. demonstrated the use of AdV-mediated delivery of short hairpin RNA (shRNA), which can inhibit gene expression, targeting VEGF to effectively attenuate VEGF levels and prevent CNV$^{[251]}$. Li et al. conducted studies showing that AdV vectors encoding Angiotensin II type 1 receptor-associated protein (AIP1), a substance that induces inflammatory neovascularization, combined with green fluorescent protein, could inhibit ocular neovascularization in mice with alkali-burned eyes$^{[252]}$. Additionally, recombinant AdV vectors expressing mouse interleukin-4 were found to alleviate laser-induced CNV in mice$^{[253]}$. AdVs can effectively deliver genes related to VEGF and inflammation for the treatment of neovascular eye diseases.

AAV

AAVs are satellite viruses associated with AdVs, belonging to the Parvoviridae family. AAVs rely on coinfection with helper AdVs for replication$^{[254]}$. Due to being a non-pathogenic virus with high transduction efficiency and low immunogenicity$^{[255]}$, recombinant AAV has emerged as an excellent delivery system with significant potential for treating neovascular eye diseases. Some researchers have utilized AAV to deliver antiangiogenic peptides and proteins, such as adiponectin peptide 1, increasing their expression in the retina.

Fig. 3. Delivery systems for neovascular ophthalmopathy.

Viral delivery

AdV

AdVs are double-stranded DNA viruses$^{[249]}$. Replication-defective AdV vectors possess several advantages, including their ample capacity for genetic material, high expression levels, and relative ease of production. However, one of the primary drawbacks of AdV vectors is that high doses in practical applications can lead to a shortened duration of gene expression$^{[250]}$. Early research by Cashman et al. demonstrated the use of AdV-mediated delivery of short hairpin RNA (shRNA), which can inhibit gene expression, targeting VEGF to effectively attenuate VEGF levels and prevent CNV$^{[251]}$. Li et al. conducted studies showing that AdV vectors encoding Angiotensin II type 1 receptor-associated protein (AIP1), a substance that induces inflammatory neovascularization, combined with green fluorescent protein, could inhibit ocular neovascularization in mice with alkali-burned eyes$^{[252]}$. Additionally, recombinant AdV vectors expressing mouse interleukin-4 were found to alleviate laser-induced CNV in mice$^{[253]}$. AdVs can effectively deliver genes related to VEGF and inflammation for the treatment of neovascular eye diseases.

AAV

AAVs are satellite viruses associated with AdVs, belonging to the Parvoviridae family. AAVs rely on coinfection with helper AdVs for replication$^{[254]}$. Due to being a non-pathogenic virus with high transduction efficiency and low immunogenicity$^{[255]}$, recombinant AAV has emerged as an excellent delivery system with significant potential for treating neovascular eye diseases. Some researchers have utilized AAV to deliver antiangiogenic peptides and proteins, such as adiponectin peptide 1, increasing their expression in the retina.
and choroid of CNV model mice. This approach represents a low-injection-frequency therapy with promise for treating wAMD. Yu et al. employed AAV8 to deliver a novel anti-VEGF molecule containing multiple VEGFR domains, resulting in sustained and safe suppression of CNV in model mice following subretinal injection. AAV vectors are often employed to deliver peptides and proteins, and their sustained efficacy can effectively reduce injection frequencies, making them advantageous for the treatment of neovascular eye diseases.

Retrovirus (rRV)

rRV are 80-130 nm viruses capable of providing efficient and prolonged gene expression delivery with high transduction efficiency. However, rRV requires dividing cells and involves random integration, which raises safety concerns. As early as 1998, some researchers constructed rRV for ocular injection of β-galactosidase, and its expression was observed in choroidal neovascular membranes. This demonstrated the potential of rRV-mediated gene delivery in choroidal neovascularization. Research by Sakamoto Taiji et al. showed that regulatory genes delivered by rRV could produce specific proteins in RPE cells, altering the angiogenic activity of these cells. This indicates the potential of gene therapy in the eye. Chen et al. found that recombinant rRV encoding mouse endostatin and mouse VEGF receptor-2 effectively inhibited HUVECs proliferation and migration in vitro and suppressed alkali burn-induced CNV in a mouse model after subconjunctival injection. rRV can efficiently deliver relevant genes for the treatment of neovascular eye diseases, playing a crucial role in gene therapy.

rLV

rLV belong to the retroviridae family, possess an RNA genome, and include integrative enzymes, reverse transcriptases, and more within their capsids, making them suitable gene therapy vectors for various ocular diseases. rLVS are highly efficient and provide sustained gene delivery. However, their high immunogenicity and safety concerns cannot be overlooked. Researchers have found that rLV delivery of short hairpin RNA (shRNA) targeting taurine upregulated gene-1 (TUG1, involved in angiogenesis and vascular remodeling of various endothelial cells) can reduce inflammatory responses in the retinal tissue of mice with oxygen-induced retinopathy, effectively lowering the incidence of retinal neovascularization. Recombinant rLVS can regulate neovascularization by delivering various factors associated with ocular neovascularization. Examples include the delivery of antiangiogenic agents like WIF1 (the canonical wingless-type MMTV integration site inhibitory factor 1), NADH-Cytochrome B5 Reductase 2 (CBR2), and miR-340-5p (a miRNA that plays a key role in mesenchymal stem cell (MSC)-mediated antiangiogenesis). Researchers have explored rLV delivery systems extensively to inhibit pathological ocular neovascularization, indicating that rLVS hold promise as a delivery system.

Non-viral delivery

Lipid nanoparticles (LNPs)

Nowadays, many In recent years, numerous studies have focused on encapsulating drug molecules in various nanodelivery systems for both invasive and non-invasive administration to treat ocular diseases. LNPs have gained significant attention in ocular therapeutic delivery systems due to their excellent biocompatibility and ability to degrade in vivo. Common lipids employed in LNPs synthesis include fatty acids, monoacylglycerols, diacylglycerols, triacylglycerols, waxes, liquid lipids, and cationic lipids. LNPs typically exhibit a spherical structure with both hydrophilic and hydrophobic moieties. In earlier studies, researchers prepared LNPs loaded with short hairpin RNA (shRNA) targeting angiopoietin-like protein 2 (ANGPTL2), a proangiogenic and proinflammatory factor in the cornea. These LNPs were found to effectively suppress corneal inflammation and CNV. In earlier studies, researchers prepared LNPs loaded with short hairpin RNA (shRNA) targeting angiopoietin-like protein 2 (ANGPTL2), a proangiogenic and proinflammatory factor in the cornea. These LNPs were found to effectively suppress corneal inflammation and CNV. In earlier studies, researchers prepared LNPs loaded with short hairpin RNA (shRNA) targeting angiopoietin-like protein 2 (ANGPTL2), a proangiogenic and proinflammatory factor in the cornea. These LNPs were found to effectively suppress corneal inflammation and CNV. In earlier studies, researchers prepared LNPs loaded with short hairpin RNA (shRNA) targeting angiopoietin-like protein 2 (ANGPTL2), a proangiogenic and proinflammatory factor in the cornea. These LNPs were found to effectively suppress corneal inflammation and CNV. In earlier studies, researchers prepared LNPs loaded with short hairpin RNA (shRNA) targeting angiopoietin-like protein 2 (ANGPTL2), a proangiogenic and proinflammatory factor in the cornea. These LNPs were found to effectively suppress corneal inflammation and CNV. In earlier studies, researchers prepared LNPs loaded with short hairpin RNA (shRNA) targeting angiopoietin-like protein 2 (ANGPTL2), a proangiogenic and proinflammatory factor in the cornea. These LNPs were found to effectively suppress corneal inflammation and CNV. In earlier studies, researchers prepared LNPs loaded with short hairpin RNA (shRNA) targeting angiopoietin-like protein 2 (ANGPTL2), a proangiogenic and proinflammatory factor in the cornea. These LNPs were found to effectively suppress corneal inflammation and CNV. In earlier studies, researchers prepared LNPs loaded with short hairpin RNA (shRNA) targeting angiopoietin-like protein 2 (ANGPTL2), a proangiogenic and proinflammatory factor in the cornea. These LNPs were found to effectively suppress corneal inflammation and CNV.
PNPs

PNPs are composed of naturally occurring or artificially synthesized biocompatible and non-toxic polymers. PNPs are generally degradable and non-immunogenic, facilitating drug delivery in vivo. Common polymers used include polylactic acid-hydroxyacetic acid copolymer (PLGA), polylactic acid (PLA), polyethylene glycol (PEG), chitosan (CS), and hyaluronic acid (HA), among others\cite{271}. Researchers have employed non-covalent zinc ion bridges between PLGA carboxyl termini and dexamethasone sodium phosphate (DSP) to synthesize a DSP delivery system. This system, coated with dense PEG and forming 200 nm spherical PNPs, allowed for control over DSP release via PLGA/PLA ratios. Subconjunctival injection of this system delivered DSP to the anterior segment of rat eyes, effectively suppressing suture-induced CNV\cite{272}. More recently, scholars have developed a novel eyedrop based on liposomes and trimethyl chitosan (TMC) for the co-delivery of insulin and siVEGF to treat alkali-burned corneas in rats. TMC coated the liposomes as a layer to prepare nanoparticles, enhancing the stability of the delivery system. This PNP delivery system significantly suppressed CNV in the rat model\cite{273}. Zhang et al. synthesized PNPs using PEG-conjugated arginine-glycine-aspartic acid (RGD) peptides and polyethylenimine (PEI) to deliver the antioxidant tanshinone IIA to the posterior segment. This delivery system achieved sustained release of tanshinone IIA, selectively accumulated in CNV lesions, and exhibited therapeutic effects\cite{274}. PNPs can utilize various polymers and modifications as needed to extend drug release times and reduce the need for intraocular injections. PNPs carrier systems offer promising therapies for neovascular eye diseases.

AuNPs

AuNPs have found widespread use in biomedical fields owing to their small size, stability, low toxicity, ease of detection, and modification capabilities. Due to their small size, AuNPs can enter blood vessels and even organelles, making them effective DDS candidates\cite{275}. AuNPs consist of an inorganic gold core and organic monolayer coatings, which have shown dose-dependent antiangiogenic effects by inhibiting VEGFR2\cite{276}. Recently, researchers synthesized Au-CS NPs that adsorbed fluorescent nanodiamonds (FNDs) (Au-CS@FNDs) and incorporated them into contact lenses. Au-CS@FNDs exhibited good antibacterial capability and antiangiogenic effects by photothermally killing human umbilical vein HUVECs, showing promise for inhibiting CRNV through photothermal therapy\cite{277}. Lu et al. demonstrated that AuNPs could exert antiangiogenic effects at the cellular level and in a laser-induced mouse CNV model, reducing the CNV lesion area by 67.9\%\cite{278}. The intrinsic antiangiogenic activity of AuNPs DDS, coupled with their enhanced antiangiogenic, anti-inflammatory, and antioxidant effects via the delivery of antiangiogenic agents, positions AuNPs as a superior treatment option for neovascular eye diseases such as wAMD.

Extracellular vesicles (EVs)

EVs are lipid bilayer vesicles released in a controlled manner from cells, with a diameter of 30-1000 nm, and are widely present in biological fluids. Exosomes, a subtype of EVs, have a diameter of 30-150 nm\cite{279}. EVs play a crucial role in mediating intercellular communication and contain various proteins, lipids, and nucleic acids. Recent research highlights EVs as naturally excellent carriers with good safety, efficiency, and targeted delivery potential for the diagnosis and treatment of ocular diseases\cite{280}. EVs can serve directly as therapeutic agents for diseases and can also act as carriers for drug delivery in disease treatment. EVs offer unique advantages, including the ability to penetrate biological barriers and play essential roles in neovascularization. For example, Shivakumar et al. utilized mesenchymal stem cell-derived EVs to encapsulate the antiangiogenic drug Bevacizumab. This system effectively reduced VEGF levels, retinal leakage, and leukostasis over a sustained period of up to two months. It significantly decreased the need for intravitreal injections in the treatment of DR in rats\cite{281}. Human umbilical cord mesenchymal stem cell-derived exosomes (hucMSC-Exo) enriched with miR-27b-3p alleviated laser-induced CNV development in a mouse model by reducing subretinal fibrosis after intravitreal injection\cite{282}. Exosome-associated AAVs exhibited enhanced retinal penetration and expression compared to AAV alone following intravitreal injection\cite{283}. EVs have been implicated in various ocular diseases including AMD, ROP and NVG\cite{284}. They hold tremendous potential for practical applications but face challenges related to mass production and storage. Therefore, EVs represent a significant focus of research to overcome these obstacles and develop more promising therapies.
for neovascular eye diseases.

Hydrogel

Injectable hydrogels are used for drug delivery due to their three-dimensional structure, minimally invasive characteristics, shear thinning, self-healing properties, and more. Shear thinning and self-healing refer to the ability of preformed hydrogels to become less viscous for injection under applied shear stress and then return to their gel-like state after shear forces are removed[285]. Shear thinning enables hydrogels to be injected through syringes to target sites, avoiding invasive surgical harm. Injectable hydrogels can be designed using various polymers, crosslinkers, and nanomaterials to control drug release rates as needed. Drugs can be loaded into the three-dimensional network structure via Schiff base reactions between the drug and gel components, allowing for slow passive drug release[286]. The Schiff base reaction involves dynamic covalent bonds between aldehyde and various nucleophilic amino groups, maintaining a dynamic equilibrium between hydrogel rupture and reformation.

Researchers have prepared injectable hydrogels through Schiff base reactions between aminated hyaluronic acid and aldehyde-functionalized Pluronic 127, loading Bevacizumab. This system sustained the release of Bevacizumab for over 7 weeks and exhibited antiangiogenic effects for up to 12 weeks in a rabbit model of persistent retinal neovascularization[14]. Some scholars have integrated the advantages of both hydrogels and microemulsions to create an injectable temperature-responsive hydrogel depot for intravitreal injection. They co-encapsulated berberine and baicalein dual drugs in a microemulsion-loaded DDS (Bor/RB-M@TRG). A single intravitreal injection of Bor/RB-M@TRG significantly inhibited CNV in a mouse model of wAMD, with the system penetrating deep into the posterior segment of the retina and remaining stable in the RPE layer for up to 14 days[287]. Injectable hydrogels can deliver antiangiogenic drugs to the posterior segment of the eye and offer excellent sustained release capabilities, resulting in effective antiangiogenic and anti-inflammatory effects in vivo. Injectable, self-healing hydrogel delivery systems provide a promising new therapy for the future treatment of neovascular eye diseases, benefiting patients.

Concluding remarks

Over the past few decades, various neovascular eye diseases, including AMD, ROP, and NVG, have inflicted significant harm on patients with eye diseases worldwide. While there are numerous therapies and emerging DDS available for neovascular eye diseases, truly effective treatments remain limited. Several factors contribute to this challenge: first, the pathogenesis of many neovascular eye diseases is not yet fully understood, and ongoing research is exploring various mechanisms; second, the presence of ocular barriers makes it difficult for delivery systems to transport drugs to the interior of the eye, particularly the posterior segment; third, controlling drug retention time is challenging, and invasive treatments can add further discomfort to patients. Currently, there is a growing number of patients with eye diseases both domestically and internationally, underscoring the urgent need to develop innovative therapies for eye disease management.

This review has delved into the pathogenesis of several common neovascular eye diseases, with a particular focus on antiangiogenic drugs (such as antibodies, aptamers, enzyme inhibitors, angiostatin, endostatin, etc.) used for targeting and managing neovascular diseases. It highlights their effects and current usage. Additionally, it explores the utilization of various DDS, including viruses, LNPs, PNPs, AuNPs, EVs, hydrogels, and more, which hold promise in enhancing therapeutic outcomes, facilitating improved drug delivery to the posterior segment of the eye, and extending drug action duration. Many DDSs exhibit substantial potential, emphasizing the urgent need for the development of novel and more effective treatment strategies for neovascular eye diseases.

Acknowledgements

This study was supported by the International Cooperation Project (No. 20220402036GH) of Jilin Province Science and Technology Development Plan Project.

Conflict of interest statement

14
The authors declare no conflicts of interest.

References


9 A. G. Kelly and D. Panigrahy, *Cold Spring Harbor Perspectives in Medicine* 2023, 13,.


Ophthalmology 2022, 129, e69.


Ophthalmology 2021, 128, E51.

72 A. Hellström, L. E. H. Smith and O. Dammann, 

The Lancet 2013, 382, 1445.

73 G. D. Hartman, N. A. Lambert-Cheatham, M. R. Kelley and T. W. Corson, 

International Journal of Molecular Sciences 2021, 22.

74 M. P. Nicholas and N. Mysore, Experimental Eye Research 2021, 202, 108363.

75 M. P. Nicholas and N. Mysore, Experimental Eye Research 2021, 202.


103 A. Barzelay, A. Lowenstein, J. George and A. Barak, *Current Eye Research* 2010, 35, 835.


20


157 L. Guo, L. Hua, B. Hu and J. Wang, *Current molecular medicine* **2023**.


21


167


22


23


204 S. C. Chi, Y. N. Kang and Y. M. Huang, Scientific Reports 2023, 13


238 A. S. Rosenberg, *Leukemia & Lymphoma* 2023, 64, 283.


<table>
<thead>
<tr>
<th>Diseases</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>wAMD</td>
<td>CNV with leakage, drusen appear; complement activation and inflammation</td>
</tr>
<tr>
<td>DME</td>
<td>Chronic hyperglycemia leads to loss of retinal vascular regulation, vascular leakage, tissue edema, and exudate of lipid and protein</td>
</tr>
<tr>
<td>PM-CNV</td>
<td>Excessive elongation of the eye axis, stretching or even rupture of retinal tissue, thinning of the choroid, which leads to retinal vascular remodeling</td>
</tr>
<tr>
<td>NVG</td>
<td>Retinal ischemia and hypoxia, upregulation of pro-angiogenesis-related factors, hypoxia-inducible factor 1-α (HIF-1α), inflammatory cytokines (IL-1β, IL-6, IL-8); progressive angiogenesis in NVI and NVA. PDR is the main cause</td>
</tr>
<tr>
<td>ROP</td>
<td>Ocular vascular developmental abnormalities due to prematurity, high oxygen exposure, infections, fundus pigmentation, and vision disorders; most common in infants born before 32 weeks of gestational age and weighing less than 1.5 kg</td>
</tr>
<tr>
<td>CNV</td>
<td>Newly formed vessels grow from the choroidal capillaries and invade the subretinal space through rupture of Bruch’s membrane</td>
</tr>
</tbody>
</table>

Table 2: Neovascular-related eye diseases therapeutic drug classes.
<table>
<thead>
<tr>
<th>Classification</th>
<th>Drugs</th>
<th>Target site of action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-VEGF antibody</td>
<td>Bevacizumab</td>
<td>VEGFA</td>
<td>[222-224]</td>
</tr>
<tr>
<td></td>
<td>Ranibizumab</td>
<td>VEGFA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aflibercept</td>
<td>VEGFA, VEGFB, PIGF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Conbercept</td>
<td>VEGFA, VEGFB, PIGF</td>
<td></td>
</tr>
<tr>
<td>Anti-VEGF aptamers</td>
<td>Pegaptanib</td>
<td>VEGF_{165}</td>
<td>[225, 226]</td>
</tr>
<tr>
<td>Enzyme inhibitor</td>
<td>Sorafenib</td>
<td>VEGFR1-3, PDGFR</td>
<td>[133, 135]</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>VEGFR</td>
<td>[136, 227]</td>
</tr>
<tr>
<td></td>
<td>Sunitinib</td>
<td>VEGFR, PDGFR</td>
<td>[228, 229]</td>
</tr>
<tr>
<td>Other inhibitors</td>
<td>Somatostatin</td>
<td>SSTR, IGF-1</td>
<td>[153, 230-232]</td>
</tr>
<tr>
<td></td>
<td>Endostatin</td>
<td>KDR/Flk-1 (VEGFR), MMP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angiostatin</td>
<td>tPA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEDF</td>
<td>Targeting ECs by PEDFR</td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>Loxoprofen sodium</td>
<td>PGSH</td>
<td>[186, 233-235]</td>
</tr>
<tr>
<td></td>
<td>Nepafenac</td>
<td>PGSH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indomethacin</td>
<td>PGSH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketorolac</td>
<td>PGSH</td>
<td></td>
</tr>
<tr>
<td>GC</td>
<td>Triamcinolone acetonide</td>
<td>GR, PD-L1, IDO1</td>
<td>[236-240]</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>GR, AP-1, NF-κB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prednisolone acetate</td>
<td>GR</td>
<td></td>
</tr>
<tr>
<td>Gene therapy</td>
<td>cDNA</td>
<td>Secretogranin III (Scg3)</td>
<td>[241-244]</td>
</tr>
<tr>
<td></td>
<td>siRNA</td>
<td>VEGF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNA</td>
<td>VEGF, CCN5 (anti-angiogenic protein)</td>
<td></td>
</tr>
</tbody>
</table>