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Title	Recent advances and future prospects: Current status and challenges of the intraocular injection of drugs for vitreoretinal diseases
Author(s)	Hashida, Noriyasu; Nishida, Kohji
Citation	Advanced Drug Delivery Reviews. 2023, 198, p. 114870
Version Type	AM
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Recent advances and future prospects: current status and challenges of the intraocular injection of drugs for vitreoretinal diseases

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Keywords: drug delivery, vitreoretinal disease, retina, vitreous, blood retinal barrier, age-related macular degeneration, diabetic retinopathy, retinal vein occlusion, retinitis pigmentosa, clinical trial

Abstract

Effective drug therapy for vitreoretinal disease is a major challenge in the field of ophthalmology; various protective systems, including anatomical and physiological barriers, complicate drug delivery to precise targets. However, as the eye is a closed cavity, it is an ideal target for local administration. Various types of drug delivery systems have been investigated that take advantage of this aspect of the eye, enhancing ocular permeability and optimizing local drug concentrations. Many drugs, mainly anti-VEGF drugs, have been evaluated in clinical trials and have provided clinical benefit to many patients. In the near future, innovative drug delivery systems will be developed to avoid frequent intravitreal administration of drugs and maintain effective drug concentrations for a long period of time. Here, we review the published literature on various drugs and administration routes and current clinical applications. Recent advances in drug delivery systems are discussed along with future prospects.

1. Introduction

Drug delivery to the retina and other posterior segments of the eye is challenging, and there is unmet medical need for retinal disease therapeutics. Blood retinal barrier (BRB) dysfunction occurs in many retinal diseases. BRB contributes to the pathophysiology of several vascular ocular diseases, including age-related macular degeneration (AMD), diabetic retinopathy (DR), retinal vein occlusion (RVO), retinopathy of prematurity (ROP), and uveitis. This pathology results in vasogenic edema, causing vision loss [1]. Vascular endothelial growth factor (VEGF) plays a major role in the pathogenesis of retinal choroidal diseases, including neovascular AMD (nAMD), DR, and diabetic macular edema (DME); thus, several drugs targeting VEGF have been developed [2-4].

Anti-VEGF therapy can prevent vision loss and even restore or improve vision in many cases. Although anti-VEGF therapy has many therapeutic benefits for retinal diseases for which no effective treatments were previously available, intravitreal injections of these drugs are necessary for delivery to the retina. The eye exists as a single compartment; thus, local administration of drugs via intravitreal injection is highly efficient. However, anti-VEGF therapy must be injected monthly or bimonthly, often over a long period of time. Complications such as intraocular inflammation, increased intraocular pressure, traumatic cataract, vitreous hemorrhage, and retinal detachment have been observed [5].

Therefore, drugs with longer half-lives and longer dosing intervals are desired for treating retinal diseases via intravitreal injection. This article describes the drug delivery system (DDS)

formulations used in ophthalmology to date and introduces drugs under development that may become available in the future.

2. The structure of the eye and its peculiarities regarding DDS

The eye is a unique tissue with a structure that complicates the effective delivery of adequate drug concentrations to target tissues. Developing DDSs for posterior eye disease is challenging because of the anatomic location and biological protective mechanisms, such as the BRB [6, 7]. The eye has a defense mechanism that limits the uptake of substances from the systemic bloodstream to maintain homeostasis, with a blood-aqueous barrier (BAB) in the anterior segment and a BRB in the posterior segment (Fig. 1). This mechanism complicates the pharmacological treatment of retinal disease [8-11]. The anterior BAB is composed of tightly bound endothelial cells in the uvea, especially in the ciliary body, and limits the influx of plasma albumin from blood vessels into the aqueous humor and the migration of water-soluble drugs. The BRB should be considered when delivering drugs to the posterior ocular region. Drug transfer from the blood to the retina is severely restricted by the tightly coupled inner and outer BRB, which limits the transfer of drugs from the systemic blood to the retina [12].

Drugs administered into the vitreous have a half-life of several hours to several days [13, 14]. By modifying the administration method and drug properties, the half-life of these drugs has been extended to a few months to a few years [7, 15, 16]. Increasing the drug concentration in the local retinal area is important for enhancing drug delivery to the retina. However, prolonging the drug's half-life and, thus, the drug concentration increases the risk of toxicity to the retina and optic nerve. Various routes of administration and types of drugs are being explored [17, 18]. There are several options for topically delivering drugs to ocular tissues, the most common of which is eye drops. Other approaches for drug delivery into the eye include subconjunctival, subretinal, and intravitreal injections (Fig. 2). Delivery via the systemic circulation through the administration of oral or intravenous therapies is another option; however, delivery efficiency to the retina is extremely low [19]. The structure of the eye and the presence of biological protective mechanisms hinder the ability of the drug to enter the retinal tissue.

3. History of DDSs in the fields of Ophthalmology

The history of DDSs in the field of ophthalmology is reviewed in this section [20, 21]. The first DDS formulation applied in ophthalmology was Ocusert, which contains the glaucoma drug pilocarpine and releases the active ingredient in the conjunctiva for a week. Ocusert was approved by the Food and Drug Administration (FDA) in the United States in 1974 [22, 23]. Agents targeting retinal disease have

been developed since the introduction of Ocusert. For example, steroids are administered in eye drops or by periocular, intravitreal and systemic injections for treating ocular inflammatory diseases. The frequency of administration, dosage, and long-term use of steroids should be carefully monitored due to the risk for systemic and local ocular adverse effects [24]. Therefore, topical administration is a more promising therapeutic strategy than systemic administration, and steroid implants have been investigated for early-stage ocular inflammatory diseases. Subtenon or intravitreal administration of triamcinolone acetonide (TA) is used to treat ocular inflammatory diseases, providing a sustained-release anti-inflammatory effect. Because the drug is administered unmodified, the local drug concentration is highest at the time of administration and decreases over time; thus, the local drug concentration is not maintained over a long period of time. Implants that maintain effective concentrations for extended periods are under development.

Vitrasert® (pSivida, now EyePoint Pharmaceuticals, Watertown, MA) and Retisert® (Bausch & Lomb, Rochester, NY) were the first-developed indwelling intravitreal implants. Ozurdex® (Allergan Inc, Irvine, CA) and Ilvien® (Alimera Sciences, Alpharetta, GA), both indwelling vitreous implants, have been commercialized in the United States [25]. Vitrasert® is a ganciclovir-containing drug used to treat cytomegalovirus retinitis and releases the drug for 5–8 months [26, 27]. Retisert® was approved in the United States in 2005 for treating noninfectious uveitis. Retisert® encapsulates 0.59 mg of fluocinolone acetonide that is stably released over 30 months [28]. Surgery is required for implant removal and replenishing the drug [24]. Steroid implants provide stable drug release and are highly effective for treating uveitis symptoms; however, many patients treated with steroids develop increased intraocular pressure and cataracts. Some patients also require filtration surgery [29]. Ozurdex® is a biodegradable vitreous implant containing dexamethasone injected into the vitreous using a dedicated device [30, 31].

Macular edema associated with RVO, DR and noninfectious uveitis can be treated with indwelling vitreous implants. Ilvien® is a biodegradable indwelling vitreous implant containing fluocinolone acetonide released over 3 years and is indicated for DME [32, 33]. Renexus®, an intraocular implant that utilizes encapsulated cell technology (ECT), was developed by Nanotech Pharmaceuticals, Inc (Hillsborough, NJ). Renexus® contains retinal pigment epithelial (RPE) cells genetically modified to secrete ciliary neurotrophic factor (CNTF), a neuroprotective factor, inside a hollow cylinder with a translucent membrane. Renexus® has been reported to have an inhibitory effect on visual acuity loss in patients with geographic atrophy (GA) associated with dry AMD [34], retinitis pigmentosa (RP), GA alone [35, 36], and macular telangiectasia (MacTel) type 2 [37]. The efficacy and safety of Renexus® for chronic retinal disease have been verified. Renexus® releases CNTF into the

vitreous through a semipermeable membrane that prevents immune cell targeting of the encapsulated cells and allows the uptake of nutrients necessary for the cells' survival. NT-503 (NCT02228304) releases soluble VEGF receptors, and NT-506 releases a platelet-derived growth factor (PDGF) antagonist; these drugs are under development for exudative AMD.

4. Method of administration

4.1. Systemic administration

The BRB is a physical barrier that hinders the transfer of drugs from the systemic circulation to the retina after intravenous or oral administration. The choroid, located directly beneath the retina, has a rich blood supply from which drugs can easily migrate into the choroidal extravascular space; however, the BRB restricts further drug migration into the retina [19, 38]. The dose of systemically administered drugs that reach the local ocular site is a few thousandths of the dose delivered despite the rich blood supply of the choroid [39]. Increasing the systemically delivered dose can increase the local ocular concentration. However, drug delivery efficiency to the retina from the bloodstream is extremely low, and specific targeting systems are needed. Efficient drug delivery systems that use liposomes and other carriers are being developed to allow a larger proportion of the drug to accumulate at the target site.

Other drug formulations with modified properties providing a sustained release effect over long periods are under development. For example, DDSs using nanosized particles [19], liposomes, and biodegradable polymer nanoparticles composed of biocompatible molecules such as polylactic glycolic acid (PLGA) [40-42], chitosan, gelatin [43], and hyaluronic acid (HA) [44] can effectively deliver drugs to target sites and enhance the therapeutic effects; these options and their attributes are under intensive investigation [45].

4.2. DDSs using eye drops

Ophthalmic eye drops are noninvasive topical treatments that are easy to administer; thus, eye drops are the ideal topical formulation for ocular drug administration (Fig 2). Efforts by pharmaceutical companies have led to the development of formulations using polyethylene glycol (PEG) and gelatin to improve tissue affinity and retention [43, 46]. Although eye drops show some efficacy in treating anterior segment lesions, they are less effective for uveitis and other eye diseases. The administered drug migrates into the eye via the cornea and conjunctiva. Therefore, eye drops are excellent for drug administration to the anterior segment of the eye, including the cornea, conjunctiva, and sclera.

However, regarding the posterior segment of the eye, the metabolic ability of the eye to rapidly expel foreign substances into the tear fluid of the nasolacrimal duct must be considered. The bioavailability of ophthalmic drugs is extremely low, and efficient drug delivery to the posterior ocular region cannot be achieved. In addition, drug properties such as molecular weight and solubility affect ocular translocation. Even if the drug permeates the cornea or conjunctival epithelium, it is rapidly expelled from the eye due to aqueous humor turnover and in the circulating blood of the uveal tissue. Dosage adjustments to achieve a therapeutic effect with eye drops are challenging because the volume of solution that can be administered to the eye is limited. There are many challenges to overcome in the design of eye drops for targeting the retina, including the necessity for sterility, the consideration of osmotic pressure and pH, and the importance of stabilizing the drug composition without compromising its activity. The bioavailability of eye drops after topical administration is low; <3% of the topically administered drug reaches the anterior chamber fluid [47]. The proportion of the drug that reaches the posterior segment is lower and is typically below a therapeutic concentration [48]. Recently, nanotechnology-based topical formulations and ophthalmic in situ gelling systems have been developed to increase intraocular of drugs migration. However, reaching the retina remains a challenge due to migration barriers, such as the outer BRB to the choroid [49]

4.3. Transscleral DDS

Since the sclera is composed of loosely connected collagen tissue and can be penetrated by macromolecules, such as antibodies, implants placed on the sclera may be capable of delivering a sustained-release drug to the retina (Fig. 2, 3). Steroids are lipophilic with low toxicity, even at saturated concentrations, making them ideal for DDS formulations. Periocular steroids can be administered by various routes, including subtenon, subconjunctival, orbital floor, trans-septal, and retrobulbar injections [50-52]. TA suspension does not require a base drug, and a 20 mg subtenon injection yields a sustained-release period of approximately 3 months [53-55]. Indications for periocular injection of TA include DME [56, 57], macular edema associated with RVO [58], and uveitic macular edema [59, 60]. Clinically, periocular corticosteroids can control macular edema with improvement observed within 4 weeks to several months. Recurrence of macular edema is common, and repeated injections are frequently required. Patients should be monitored for cataract progression and ocular hypertension, and upper eyelid ptosis may also occur [52, 61, 62]. Chronic progressive retinal disease requires long-term drug treatment. Capsule-type drug-releasing devices implanted on the sclera or a sheet-type device have been shown to be effective in addressing the insufficient drug delivery levels to the posterior segment

with eye drops and reducing the risks associated with invasive intraocular injections and the side effects of drug delivery to the vitreous body [63-65].

4.4. Intravitreal DDSs

In general, only a small fraction of systemically administered drugs reach the retina. Regarding DDSs for retinal disease, increasing the total dose is the only way to increase the concentration of the drug in the eye. However, considering the eye is a pharmacological compartment and a closed space, delivering the drug locally is an attractive approach. Administering the drug directly into the vitreous body can reduce the complications of systemic delivery, and local concentrations can be increased (Fig. 2). The retina is a nerve tissue that is difficult to approach directly, and the vitreous can be a good reservoir for drugs for treating posterior segment diseases. Furthermore, since the vitreous gel is composed of HA, in non-avitreal eyes, there is little convection in the vitreous, and high-molecular-weight drugs remain in the eye for relatively long periods. Conversely, clearance is enhanced in avitreal eyes. Many drugs have been developed that take advantage of the vitreous body anatomy. Anti-VEGF therapy, in particular, has become the mainstay of exudative AMD treatment. The first report of an anti-VEGF agent for nAMD was a 2006 retrospective study of 226 AMD eyes treated with a single intravitreal 1.25 mg dose of bevacizumab that improved mean visual acuity and central foveal retinal thickness 12 weeks after injection [66]. Although there have been many reports on the pharmacokinetics of intravitreal anti-VEGF drugs, few studies have rigorously analyzed how these drugs penetrate/diffuse through the internal limiting membrane and Bruch's membrane to reach the choroid [67, 68]. The permeability of anti-VEGF drugs was analyzed in highly polarized human RPE cells, and the effects of bevacizumab, ranibizumab, and aflibercept were compared. The results showed that ranibizumab, bevacizumab, and aflibercept had high penetration; however, ranibizumab and aflibercept demonstrated higher neutralization of VEGF than bevacizumab [69-71] . Considering these factors, the molecular weight of drugs and binding affinity to VEGF may have a significant impact on their anti-VEGF effect [72].

Many drugs have subsequently been developed and evaluated in clinical trials. Nondegradable and biodegradable implants to increase drug concentrations in the ocular region have been developed

and are currently being evaluated in clinical trials. A method to prolong the length of time the drug remains in the eye involving the addition of a gelling agent to the vitreous is also under development. This drug, IBI-20089 (Icon Bioscience, Inc., Watertown, MA) provides a sustained-release effect due to the mixture of TA with Verisome, a base drug that reacts with the vitreous humor to form a gel. The eye is a closed space; thus, administered drugs are unlikely to rapidly disappear from the eye and enter the systemic circulation. However, there is no clear evidence regarding the systemic safety of the intravitreal injection of anti-VEGF drugs, which is a topic of continuing debate. Thulliez M et al. conducted a systematic review and meta-analysis comparing the incidence of systemic adverse events in patients with nAMD, DME, or RVO treated with intravitreal injections of anti-VEGF agents versus control treatment (including no treatment). No increased risk for systemic adverse events (SAEs) associated with the treatment was found [73]. However, intraocular injections are invasive and can cause intraocular inflammation, bleeding, cataracts, and retinal detachment [74, 75].

4.5. Suprachoroidal DDS

The suprachoroidal space (SCS), which is the potential space between the sclera and choroid, provides a useful space for drug delivery to the posterior segment of the eye. SCS can be visualized using optical coherence tomography (OCT) and other examination equipment, and drugs can be delivered safely and relatively easily if administered via a microneedle [76]. Intravitreal administration is excellent for targeted drug delivery; however, the surgical invasion is significant. Although intravitreal injection is an easy approach, complications such as cataracts, increased intraocular pressure, and uveitis must be considered [19]. A simple surgical technique is used to insert a catheter or cannula with easy access to the SCS [77, 78]. TA and anti-VEGF drugs are administered using a hollow microneedle or similar device for direct injection into the SCS [79-81]. Many clinical trials, including suprachoroidal TA for RVO: TANZANITE (NCT02303184), suprachoroidal space alterations following delivery of TA: post hoc analysis of the phase 1/2 HULK study of patients with DME: HULK (NCT02949024), suprachoroidal CLS-TA plus intravitreal aflibercept for DME: a randomized, double-masked, parallel-design, controlled study: TYBEE (NCT03126786), efficacy and safety of suprachoroidal CLS-TA for macular edema secondary to noninfectious uveitis: Phase 3 randomized trial: PEACHTREE (NCT02595398), extension study of the safety and efficacy of CLS-TA for treatment of macular edema

associated with noninfectious uveitis: MAGNOLIA (NCT02952001), and suprachoroidal CLS-TA for noninfectious uveitis: an open-label safety trial: AZALEA (NCT03097315), are underway. It is important to be cautious about its effectiveness, safety, biodegradability, immunogenicity, and inflammation, and further analyses of more cases are needed to clarify these factors.

4.6. Subretinal DDS

Although surgery is required to deliver the drug directly under the retina using a surgical microscope, subretinal DDS can be effective because it allows the drug to reach the cells of the subretinal space and retinal layer directly. In many gene therapies, the administration route involves the subretinal administration of drugs, such as viral vectors. Although rejection is a concern in PRE cell transplantation [82], successful autologous transplantation has been reported [83, 84]. Embryonic stem (ES) and induced pluripotent stem (iPS) cells are used as biomaterials for cell therapy; suspension cell transplantation using ES cells differentiated into PRE cells and ES cell-derived RPE sheet transplantation have been reported [85, 86]. The transplant of cells, such as iPS cells, can also loosely be considered a DDS approach. Cell transplantation is an effective potential therapy for repairing retinal tissue, which is unable to self-renew, and in 2014, a subretinal transplantation of RPE cell sheets fabricated from iPS cells was performed on an AMD patient [87]. However, the transplant procedure is invasive and requires a vitrectomy. Therefore, it is desirable to establish a minimally invasive and effective method for transplanting cell sheets into the narrow space beneath the retina. Subsequently, cell transplantation approaches involving the subretinal injection of a suspension of iPS cell-derived RPE cells induced from iPS cells have been investigated [88].

4.7. Gene transfer using viral vectors

4.7.1. Viral vectors for gene therapies

The two predominant viral vector systems are adenovirus-based vectors with high transduction efficiency and retrovirus vectors that integrate into the genome and provide permanent protein

expression. Adeno-associated virus (AAV) is the most widely used viral vectors in gene therapy. They have the characteristics of long-term gene expression, high safety, and the ability to introduce genes into nondividing cells, such as neurons. Subretinal administration is often used in human clinical trials because sufficient gene expression cannot be obtained by intravitreal administration in large animals. To increase the efficiency of fast-acting gene transfer, several AAV vectors, including self-complementary AAV vectors [89], tyrosine-capsid mutant AAV8 vectors [90], and the AAV2.7m8b vector [91, 92], have been developed, which efficiently express genes in the retina after intravitreal administration. Genetically modified AAV vectors are considered highly safe because they have an extremely low likelihood of integration into chromosomes and exist independently within the nucleus, thus avoiding insertional mutations. However, there are disadvantages, such as weakened expression with cell division, limited gene transfer, and time-consuming gene expression. Moreover, the presence of neutralizing antibodies against AAV and undesired immune responses and toxicity following a high dose or repeated administration of AAV via both subretinal and intravitreal injections have been reported in primate studies and clinical trials [93, 94]. Although AAV vectors are being used for therapeutics, some aspects of AAV use remain under investigation, such as gene–vector compatibility and the selection of promoters for cell-specific gene expression (Fig. 4).

4.7.2. Clinical trials using viral vectors

Gene therapy is a promising approach for treating inherited retinal degenerative diseases such as RP. The main focus is gene transfer efficiency and target cell specificity, and new studies are being published daily. Efficient gene transfer to the mouse retina was first reported in 1994 [95]. The therapeutic efficacy of gene therapy in rd mice, a mouse model of RP [96], and various other animal models of disease has been reported [97, 98]. In the field of ophthalmology, clinical studies evaluating gene therapies for retinoblastoma [99], Leber congenital amaurosis (LCA) [100-102] and choroideremia [103] have been conducted; the clinical protocol of the first gene therapy approach for AMD was reported in 2001 [104]. The result of a phase I clinical trial was reported in 2006 [105]. Clinical trials are ongoing to evaluate incorporating soluble VEGF receptor-1 (soluble flt-1) into AAV vectors (NCT01494805, NCT01024998 ; completed), the subretinal administration of an AAV8 vector (RGX-314) carrying a gene encoding a ranibizumab-like protein (NCT03066258; phase 1/2 study), and the

intravitreal administration of the AAV.7m8 vector (ADVM-22) expressing aflibercept (OPTIC study, NCT03748784; phase 1 study) (Table 1). ATMOSPHERE (NCT04704921) and AAVIATE (NCT04514653) are ongoing phase 2b/3 studies evaluating RGX-314 (Table 1).

Studies have reported neurotrophic factors, such as human pigment epithelium-derived factor and CTNF, as gene therapy for retinal cell protection with a protective effect on neurons [106, 107]. Optogenetics is a technology that controls the activity of cells with light and enables the artificial depolarization of neurons by light stimulation through the expression of channelrhodopsin-2 (ChR2) in neurons [108]. Basic research on controlling neurons with light and the development of therapeutic approaches using this technology is becoming increasingly active [109, 110]. Retinal ganglion cells (RGCs) are often preserved in RP, even in an advanced state of photoreceptor cell loss. The introduction of the *ChR2* gene into the remaining RGCs can generate new action potentials induced by phototropic stimulation [110, 111]. After preclinical studies in large experimental animals [112], the first clinical trial of gene therapy using optogenetic technology was initiated in 2016 (NCT02556736). The PIONEER study (NCT03326336) was conducted to evaluate the safety and efficacy of visual restoration techniques using optogenetics and light stimulation goggles in patients with advanced RP [113]. Currently ongoing/completed clinical trials using viral vector-based gene therapies are listed in Table 1, 2.

4.8. Controlled-release DDSs

4.8.1. Passive targeting

Controlled-release DDSs facilitate both active and passive targeting (Fig.3) [114]. Passive targeting DDSs can be used in cancer to take advantage of the enhanced vascular permeability of neovascular vessels in the tumor and surrounding tissue to deliver drugs to the target site. These targeting mechanisms are under development using anticancer drugs against various tumor cells. Similar to in tumor tissue, sites of inflammation and neovascularization in the retina are hyperpermeable and allow administered drugs to leak out of blood vessels; thus, passive targeting is a potential approach for treating retinal disorders [115-117]. Most systemically administered drugs are metabolized in the liver and kidneys, resulting in a rapid decrease in blood drug levels and failure to maintain effective blood

drug concentrations. Therefore, passive targeting drugs with enhanced blood retention capabilities have been developed. For example, liposomes, first reported in 1964 by Bangham et al., are an excellent DDS preparation. Liposomes encapsulating anticancer and antifungal drugs have been developed in Europe and the U.S. and are already in clinical use [118, 119]. Most of these approaches modify the liposome surface structure to enhance blood retention. Thus, the drug is less likely to be cleared from the blood, and an effective blood drug concentration is maintained for a longer period. Liposomal steroids and liposomal amphotericin B are typical liposome formulations [120, 121]. Research on these lipid-based microparticles has made great progress and has contributed to advanced medicine. Passive targeting by using the enhanced permeability and retention (EPR) effect [122], which allows macromolecules to accumulate in tumors for a long time, is the central concept in DDSs. The development of nanoparticle-based DDS formulations such as liposomes and micelles, is underway in conjunction with advances in nanotechnology [123, 124].

In recent years, nanoparticle-based DDS (nano-DDS) has become a fundamental technology in the development of macromolecular drugs, such as nucleic acids and genes. Advances in lipid nanoparticle (LNP) and RNA technologies have led to the practical application of ONPATTRO® (Alnylam Pharmaceutical Inc., Cambridge, MA, US), the world's first siRNA drug approved in the United States in 2018 and mRNA vaccination against COVID-19 [125, 126]. In ophthalmology, the delivery of mRNA using LPNs to the posterior ocular regions, such as RPE, Müller glia, and photoreceptors, is also being validated [127]. In real-world clinical practice, the lipoformed steroid Limethasone® (Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) is used to treat rheumatoid arthritis in Japan. Liposomes encapsulating the light-sensitive substance verteporfin have been used in ophthalmology for photodynamic therapy (PDT) and have shown excellent therapeutic effects in AMD with subfoveal choroidal neovascularization (CNV).

4.8.2 Active targeting

Active targeting involves DDSs that target specific molecules (e.g., cell surface antigens, sugar chains and receptors) with pinpoint accuracy. Research has been conducted on nanocarriers using exosomes,

which are extracellular vesicles (EVs) that carry and transfer various biomolecules. Exosomes are promising DDS carriers owing to their high biocompatibility, low toxicity, and high tissue penetration [128-130]. However, exosome-based active targeting has not been extensively studied in the field of ophthalmology. Pollaris et al. analyzed the uptake of ligand-modified exosomes as nanocarriers in a mouse model of laser-induced choroidal neovascularization. This study demonstrated that systemically administered drug can pass through the BRB and reach the retina, whereas intravitreally administered drug selectively accumulates in the CNV, suggesting the possibility of active targeting in the treatment of AMD [131]. For example, the interaction between vascular endothelial cells and leukocytes at the site of inflammation plays an important role in the pathogenesis of inflammation. Thus, E-selectin, specifically upregulated on cell surfaces at sites of inflammation, is a good molecular target for treating inflammatory diseases such as uveitis [132]. E-selectin and P-selectin are upregulated on vascular endothelial cells at inflammation sites. Inflammatory cells bind to vascular endothelium via sialyl Lewis X (SLX), a carbohydrate ligand on the molecule's surface, and accumulate at the site of inflammation due to chemokine signaling. Target-directed liposomes are representative carriers for active targeting and have been developed to target both E-selectin expressed on inflammatory vascular endothelial cells and SLX expressed on leukocytes. The molecular dynamics of SLX-conjugated liposomes have been evaluated in an experimental mouse model of autoimmune uveitis. Target-directed liposomes have been shown to accumulate in inflammatory areas with high E-selectin expression levels. In addition, attempts have been made to develop indocyanine green (ICG)-encapsulated liposomes for light-induced controlled release in ocular tissues [133, 134]. Using liposomes with enhanced target directivity may enable the development of inflammatory site-specific DDSs with reduced systemic side effects [114, 135].

In the field of oncology, with the progress of antibody production technology, drugs using antibody-drug conjugates (ADC), which are bioconjugates of monoclonal antibodies and cytotoxic drugs (payload) that are attached using an appropriate linker, have been developed [136]. ADC was first proposed in the 1970s and was formerly called missile therapy. Previously, the antibodies produced were the immunogenic mouse antibodies, and the linker technology to bind anticancer drugs to the antibodies was under development. Therefore, ADC had not reached the clinical application phase. However, currently, ADC development is rapidly gaining momentum owing to innovations in antibody production technologies, such as the development of humanized antibodies, and the linker technology is also getting

advanced [137]. Nine ADCs were launched by August 2020, and approximately 70 more are currently in clinical trials. Most of these have been developed for the treatment of cancer. In addition to ADCs, other treatment options, such as radioimmunotherapy are available [138, 139]. In the future, breakthroughs in immunotherapy can be expected from advancements in the research and development of immunomodulation with the DDS formulations and next-generation antibody drugs.

5. DDSs for targeting ophthalmic diseases

5.1 Neovascular age-related macular degeneration (nAMD)

AMD is the most common cause of irreversible central vision impairment in older populations despite the wide availability and use of anti-VEGF (Anti-vascular endothelial growth factor) therapy [140-142]. nAMD is a progressive form of AMD and is a potential cause of rapid and severe vision loss. It is caused by uncontrolled growth of abnormal neovascular vessels under the macula, leading to exudative leaks, retinal edema, inflammation, and fibrosis [143]. Approximately 20 million people worldwide are affected by nAMD, making it the leading cause of vision loss in people over the age of 60, and the number of patients is expected to increase as the global population ages [144-146]. The anti-VEGF drugs used in ophthalmology are bevacizumab (Avastin ® ; Genentech, South San Francisco, CA; off-label use), ranibizumab (Lucentis ® ; Novartis, East Hanover, NJ/Genentech, South San Francisco, CA) [3, 147], aflibercept (Eylea ®; Regeneron Pharmaceuticals, Tarrytown, NY) [4], and, most recently brolucizumab (Beovu ®, Novartis Pharmaceuticals Corporation) [148]. Pegaptanib (molecular weight 50,000) is a DDS formulation with 40 kDa PEG terminally attached to increase retention in the eye; this drug has an intravitreal half-life of approximately 10 days [149].

Ranibizumab was evaluated in the MARINA, ANCHOR, and PIER studies, and aflibercept was evaluated in the VIEW 1 and VIEW 2 studies. Brolucizumab was approved following the results of the HAWK and HARRIER clinical trials. Anti-VEGF drugs have revolutionized the treatment of AMD, successfully reducing AMD-associated blindness by ~50–72% [4, 150, 151]. Ranibizumab (molecular weight 48000) and aflibercept (molecular weight 115000) are high molecular weight drugs with a relatively long intravitreal half-life of approximately one week. Broadly, these intravitreal treatment approaches can be considered DDS products that inhibit rapid drug discharge. The effect of these drugs in AMD is sustained for 1 to 2 months when a dose 1000 times higher than that required for an

inhibitory effect is administered. Since intravitreal administration is an invasive treatment equivalent to surgery, longer-lasting pharmacological effects or a less invasive method of administration is desired. Brolucizumab is a humanized single-chain antibody fragment with a small molecular weight of 26,000, improving retinal penetration and providing increased dosing (6 mg/mL) for higher intraocular durability [152-154]. The results of the HAWK and HARRIER studies showed that brolucizumab provides better control of intraretinal, subretinal, and sub-RPE fluids than aflibercept. Although the occlusion rate in polypoidal choroidal vasculopathy (PCV) is high, there have been many reports of intraocular inflammatory complications, such as retinal vasculitis and retinal vascular occlusion [155-158]. The strong effect on the choroid may be related to the development of outer retinal or GA, which requires long-term attention and continuous monitoring after administration [159]. Recently, faricimab (Genentech, South San Francisco, CA), a bispecific antibody that binds VEGF-A and angiopoietin-2 (Ang-2), has also become available (NCT01796964). The TENAYA (NCT03823287) and LUCERNE (NCT03823300) nAMD studies indicated that the Ang-2-inhibitory effect of faricimab may contribute to prolonged dosing intervals [160]. Ang-2 is involved in the pathogenesis of PDR and DME, and faricimab may have excellent disease control potential as it inhibits not only VEGF but also Ang-2 [161]. Abicipar pegol is a PEGylated 14KDa fusion protein with an ankyrin repeat (DARPin), a molecular weight of 34,000 and an intravitreal half-life of approximately 13 days. In a Phase III study, extending the frequency of intravitreal Abicipar pegol injections to every 12 weeks resulted in fewer injections, visual improvement, and noninferiority compared to ranibizumab. However, this drug has not been approved by the FDA due to the significant risk of severe intraocular inflammation [162-164]. Currently clinical trials for therapeutic agents in posterior segment of the eye are listed in Table 1.

A large volume is required for the sustained release of water-soluble low-molecular-weight and high-molecular-weight protein formulations; thus, developing an intraocular implantable formulation with sustained-release capabilities is challenging. Several solutions to this problem are under investigation, including using a port delivery system (PDS) involving a reinjectable device or extraocular reinjection devices (microelectromechanical system: MEMS), such as osmotic pumps, with an extraocular drug reserve. Another method is to modify the vitreous cavity environment using a vitreous substitute or a gelling agent to delay drug clearance from the eye. The FDA approved Susvimo™ (Genentech, South San Francisco, CA), the first port delivery system (PDS) for continuous delivery of ranibizumab, after the conclusion of the ARCHWAY study (NCT03677934) (Table 1).

Susvimo™ is implanted through a 3.2 mm scleral incision site with a subconjunctival port for additional drug infusion. The large device used may be associated with intraocular inflammation, vitreous hemorrhage, and cataracts resulting from direct contact with the port [165, 166]. However, as the next generation of controlled release, Susvimo™ provides sustained ranibizumab therapy for approximately one year. The PDS is surgically implanted and filled with ranibizumab, which is delivered into the vitreous cavity through the sclera. The PDS is also refillable [152, 165, 167-169]. Low molecular weight compounds have no intraocular retention and require a sustained release formulation. Sunitinib is a multitarget receptor tyrosine kinase inhibitor that inhibits VEGF-A and PDGF activity. Sunitinib demonstrates potent anti-VEGF activity, inhibiting the intracellular signaling capabilities of all VEGF receptors. The ALTISSIMO (NCT03953079) trial is currently evaluating the administration of a sustained-release formulation of sunitinib encapsulated in a biodegradable polymer (PLGA); in this approach, the drug is released into the vitreous of AMD patients (Table 1) [170]. OTX-TKI (Ocular Therapeutix Inc., Bedford, MA), an investigational bioresorbable hydrogel implant incorporating axitinib, is being evaluated in early-stage clinical trials for the treatment of exudative AMD (Table 1) and is likely to become available as a treatment option in the future.

5.2. Dry AMD

No effective treatment currently exists to slow disease progression in an estimated eight million patients with GA [171]. The development of dry AMD is associated with oxidative stress and abnormalities in the complement system. Oxidative stress activates the complement system, resulting in phagocytosis by macrophages and microglia, ultimately leading to RPE degeneration [172]. Genetic mutations in factors affecting complement C3 activation (CFH, CFI, and CFB) are strongly associated with an increased risk of AMD [173], and clinical trials are ongoing for the suppression of GA [174-176]. Clinical trials (NCT04435366) on avacincaptad pegol (ACP), a novel complement C5 protein inhibitor, are also underway to treat GA. Currently ongoing/completed clinical trials for dry AMD are listed in Table 3.

5.3. Diabetic retinopathy (DR) and diabetic macular edema (DME)

DR and related DME are the leading cause of vision loss worldwide, and DR is the leading cause of preventable blindness among working-age adults in the U.S. [140, 177, 178]. DME affects approximately 21 million people worldwide, causing vision loss [179]. In DR, vascular injury and angiogenesis result in the leakage of blood and plasma components into the retina. This leakage partially disrupts the blood supply to the retina and causes edema. In DME, leakage from damaged blood vessels occurs in the macular region and causes edema. As the prevalence of diabetes is increasing, so is the number of DME patients [180]. Untreated DME can cause blindness and reduce patient quality of life; there is a significant unmet need for effective and durable therapies for DME [181]. DME is a multifactorial disease characterized by increased retinal vasculature permeability. Thus, identifying novel targets outside of the VEGF pathway may allow the promotion of vascular stability, prolonging the effect of therapy and improving patient outcomes. Anti-VEGF therapy is the current first-line standard of care for treating DME and nAMD; this therapeutic approach is also a valid treatment option for proliferative DR [140, 182, 183]. Regarding DME, ranibizumab was evaluated in the REVEAL and RESTORE trials, aflibercept by the VISTA and VIVID studies, and brolucizumab in the KESTREAL (NCT03481634) and KITE (NCT03481660) clinical trials[184-188]. The KITE (NCT03481660) and KESTREL (NCT03481634) studies demonstrated noninferiority in visual acuity improvement in DME patients treated with 6 mg of brolucizumab versus 2 mg of aflibercept. Phase III clinical trials, PAVILION (NCT04503551) and Pagoda (NCT04108156), are underway to expand the indication of ranibizumab PDS to include DR and DME (Table 1) [189]. In addition, Ang-2 upregulation has been implicated in the etiology of DME and other retinal vascular diseases. Accordingly, dual-pathway inhibition via Ang-2 and VEGF-A blockade is effective for treating DME. The efficacy of faricimab in patients with DME has been demonstrated in the YOSEMITE (NCT03622580) and RHINE (NCT03622593) phase III international clinical trial [190].

5.4. Retinal vein occlusion (RVO)

RVO inhibits venous perfusion, resulting in retinal hypoxia and increased capillary pressure on the occluded, disrupting the BRB. At the end stage of the condition, the ischemic retina in the occluded area produces VEGF, increasing vascular permeability and prolonging and worsening the macular edema. Anti-VEGF therapy is necessary as subcentral foveal serous retinal detachment decreases visual function. Ozurdex® (Allergan Inc, Irvine, CA) was originally developed to treat RVO-associated macular edema [25, 30]. Ranibizumab is the standard of care for intravitreal administration following the

BRAVO and CRUISE studies, and aflibercept is the standard of care following the VIBRANT (NCT01521559), COPERNICUS (NCT00943072), and GALILEO studies (NCT01012973) [191-197]. Phase III clinical trials evaluating faricimab in RVO ((COMINO (NCT04740931) and BALATON (NCT04740905)) are ongoing, including an extension study for nAMD and DME. KSI-301 (Kodiak Science, Palo Alto, CA) significantly prolongs the half-life of drugs in the vitreous body with a proprietary antigen biopolymer conjugate platform. KSI-301 is an anti-VEGF biopolymer complex with a molecular weight of 950 kDa, which is a high molecular weight. The BEACON (NCT04592419) trial evaluating the use of KSI-301 for RVO is currently underway (Table 1). Clinical trials evaluating TLC399 (NCT03093701) and AR-115-CF1 (NCT 03739593) for RVO-associated macular edema are also ongoing (Table 1).

5.5. Hereditary retinal disease

5.5.1. Leber's congenital amaurosis (LCA)

Leber's congenital amaurosis (LCA), first described by Leber in 1869, is a disease analogous to RP in which vision is severely impaired from early life [198]. Mutations in over 20 genes causing LCA have been identified, most of which are inherited in an autosomal recessive manner. CEP290 gene abnormality is the most frequent cause of LCA, accounting for approximately 15% of all cases. The second most frequent causes are GUCY2D and CRB1 gene abnormalities. LCA patients have a prognosis, and there are no effective clinical treatments. Acland et al. transferred the normal RPE65 gene into RPE cells in the canine LCA2 model using an AAV vector and reported marked therapeutic effects [199]. Several human clinical trials involving gene therapy for LCA have been conducted since 2007, most of which focused on RPE65 (LCA2) gene abnormalities [100-102]. The clinical efficacy of gene therapy has been confirmed in long-term studies [94, 200]. The therapeutic efficacy was demonstrated in a phase III clinical trial (NCT00999609) (Table 2) [201]. Based on the results of this trial, Voretigene neparvovec-rzyl (Luxturna™: Spark Therapeutics, Inc., Philadelphia, PA) was approved by the FDA, representing the first gene therapy approved in the field of ophthalmology. A clinical trial (NCT04516369) evaluating Luxturna™ is also ongoing, and long-term results have been reported [202, 203]. Trials evaluating other gene therapies (NCT03913143) using antisense oligonucleotides (QR-110) have been initiated for CEP290 (LCA10) genetic abnormalities (Table 2) [204]. Editas Medicine, Inc. (Cambridge, MA, USA)

conducted a clinical trial (BRILLIANCE: NCT03872479) in patients with LCA10 with a mutation in the *CEP290* gene using EDIT-101, designed to repair the IVS26 CEP290 mutant allele by AAVCRISPR/ Cas9-mediated genome editing therapeutics. However, only 3 of 14 patients had improved vision at high doses. Among patients with the IVS26 CEP290 homozygous mutation, two of three patients showed a response. Nonetheless, as there are only approximately 300 patients with this mutation in the U.S., they have abandoned in-house development and are looking for a partner.

5.5.2. Retinitis pigmentosa (RP)

RP is an inherited degenerative retinal disease characterized by progressive night blindness, afferent visual field constriction, and visual acuity loss. This disease begins in young adulthood, progresses slowly, and leads to severe vision loss in middle-aged and older individuals. Since the rhodopsin gene specifically expressed in photoreceptor cells was first reported as the causative gene for autosomal dominant RP, over 80 causative genes have been reported [205, 206]. Gene therapy has been used to treat patients with RP GTPase regulator (RPGR) gene defects in an autosomal recessive form of RP to supplement the cells carrying the abnormal gene with a normally functioning gene. Gene therapy using a subretinally injected AAV vector carrying the normal RPGR gene has also been reported [207]. A Phase 2/Phase 3 trial evaluating this approach is underway (NCT03116113) (Table 2). A phase 1/phase 2 study (NCT03328130) using an AAV vector to treat PDE6B gene abnormalities causative of an autosomal recessive form of RP is also ongoing (Table 2).

Gene editing technology with the AAV-CRISPR/Cas9-mediated system is also being evaluated at the experimental animal level [208]. Genome editing by mutation replacement using genome-editing technology may become a curative treatment for many genetic diseases, as it is not influenced by the size or genetic form of the target gene. Therefore, this technology has the potential to treat a wide range of hereditary diseases. Genome-edited gene therapy in animal models of inherited retinal dystrophy has also been reported [209, 210]. However, there are problems, such as low efficiency of genome editing, the introduction of unexpected mutations in similar sequences in the genome by illegitimate translation (off-target effects), and translation reinitiation/leaky scanning, in

which translation is initiated from a position other than the original AUG. Further technological innovation is needed to address the issues of specificity and safety [211, 212]. In addition, clinical trials have been initiated for the surgical transplantation of iPS cell-derived RPE cell sheets under the retina in Japan.

5.5.3 Choroideremia

Choroideremia is an X-chromosome recessive disorder caused by a functionally null mutation in the choroideremia gene encoding Rab escort protein-1 (REP-1). The disease begins in childhood, and the associated chorioretinal atrophy progresses slowly. Patients develop night blindness from early childhood. Progressive visual field and vision impairment are present; however, visual acuity often remains normal until relatively late in life [213, 214]. A phase 1/2 (NCT01461213) study of AAV vectors carrying the REP-1 gene administered subretinally in the macula was initiated in 2012, and the results have been reported [103, 215]. Subsequently, several phase 1/2 and phase 2 clinical trials have been initiated and reported, including NCT02077361, THOR (NCT02671539), NCT02553135, GEMINI (NCT03507686), REGENERATE (NCT02407678), and NCT02341807 [216-218] (Table 2). A phase III study STAR (NCT03496012) is also ongoing [219] (Table 2).

5.6. Retinopathy of prematurity (ROP)

Retinopathy of prematurity is a vasoproliferative disease of the developing retinal vessels in preterm infants, which is a major cause of blindness in children, for which neonatal treatment is important. Although advances in perinatal management have reduced the frequency of blindness caused due to ROP in developed countries, the number of severe ROP cases has not decreased because more premature infants have been saved [220]. Cryotherapy has been the traditional treatment for ROP; however, retinal photocoagulation is now being used based on the treatment criteria mentioned in the Early Treatment of ROP (ETROP) study (NCT00027222) [221]. In 2011, a multicenter prospective randomized controlled trial (BEAT-ROP study: NCT00622726) was conducted in the United States to report the results of the use of anti-VEGF drugs for medical therapy [222]. The recurrence rate was significantly lower in the bevacizumab vitreous group than in the photocoagulation group in cases of Zone I stage 3 plus disease but was not significantly different in posterior Zone I plus disease. International randomized clinical trials followed, and the 2019 RAINBOW study (NCT02375971) compared ranibizumab vitreous injection with photocoagulation and reported that ranibizumab vitreous injection was as effective or more effective than photocoagulation [223]. An international clinical trial

(FIRELEYE study: NCT04004208) using aflibercept has been completed and the results have been reported [224].

5.7. Uveitis

The history of DDS as a whole overlap with the history of DDS for uveitis. Development in DDS began with the use of steroids and progressed to the control of inflammation using immunosuppressive agents. To reduce the complications associated with long-term and high-dose steroid use, treatment has shifted to the use of immunosuppressive agents, such as antimetabolites (methotrexate, azathioprine, and mycophenolate mofetil), calcineurin inhibitors (cyclosporine and tacrolimus), and alkylating agents (cyclophosphamide and chlorambucil) [225]. Uveitis has several types; however, molecular targeted therapy using biologics targeting various inflammation-related factors, which are key players in inflammation, has become the mainstream treatment. Tumor necrosis factor (TNF)-α is a central factor in various inflammatory responses in the pathogenesis of uveitis. Several TNF inhibitors, including etanercept, infliximab, certolizumab, pegol, adalimumab, and golimumab, have been developed, and their clinical uses have been reported. The effectiveness and safety of infliximab in treating Behçet's disease with refractory uveoretinitis have been demonstrated in clinical trials [225]. The effectiveness of adalimumab, a humanized TNF-α monoclonal antibody, has been demonstrated in the treatment of noninfectious uveitis, providing a beneficial treatment option for uveitis other than steroid and immunosuppressive therapy [226, 227].

Uveitis often occurs in conjunction with collagen diseases, such as rheumatoid arthritis and inflammatory bowel disease, and biological agents used to treat these diseases are also used to treat uveitis. There are biological agents that target inflammatory cytokines other than TNF, such as tocilizumab and sarilumab targeting IL-6 and gevokizumab targeting IL-1β. Many other drugs are currently undergoing clinical trials, such as abatacept, which inhibits the CD80/86:CD28 co-stimulatory pathway in activated T cells; sirolimus (mammalian target of rapamycin (mTOR): NCT03711929); rituximab (targeting B cells); and filgotinib (Janus kinase (JAK) inhibitor:

NCT03207815) [229]. The use of DDSs has provided effective treatment strategies for uveitis, which was previously treated solely with steroids [229].

6. Future directions

Drug delivery to retinal tissue has advantages and disadvantages from a pharmacological perspective. The vasculature and nervous system of the retinal tissue limit delivery. Barrier mechanisms such as the BRB also hinder drug transfer to ocular tissues after systemic administration, complicating the delivery of effective drug concentrations. However, the eye is ideally suited for the local administration of drugs because it is a single-compartment organ, a feature that provides pharmacological advantages for drug administration. A single dose of a highly concentrated drug can maintain the effective drug concentration for a certain period. Thus, research has focused on local rather than systemic drug delivery.

Initially, efforts were focused on the local delivery of steroids, which are easy to formulate. However, because VEGF is involved in the pathogenesis of many forms of vitreoretinal disease, a major paradigm shift is underway with the development of drugs centered on anti-VEGF agents. Since vitreoretinal diseases encompass a large population of patients (e.g., those with AMD, DR, DME and RVO), pharmaceutical companies have vigorously pursued drug development from a commercial standpoint. This effort has led to the clinical application of various anti-VEGF drugs based on numerous clinical trials. After the development of anti-VEGF drugs, the commercial market has expanded significantly. Although progress is being made in the development of drugs with stronger inhibitory effects and drugs with longer-lasting inhibitory effects, the adverse effects of frequent intravitreal injections and the associated cost burdens on patients are significant. The risk of infection and other complications associated with drug administration is also high.

Superior technologies are being developed to overcome this problem, and many clinical trials are underway. The development of new molecularly targeted drugs and new delivery systems is expected to achieve more effective drug delivery in the future (Fig. 3). The application of gene therapy and other therapies has enabled the development of therapies for previously untreatable inherited retinal diseases. The advent of gene editing technology will allow for more precise gene modification and transfection approaches.

Considerable research into numerous DDS formulations remains ongoing. Although there will be various hurdles to clinical application, the development of carriers, various molecularly targeted drugs, synthetic chemicals and noninvasive delivery technologies will revolutionize ocular drug delivery.

Figure legends

Figure 1. Schematic illustration of the blood–aqueous barrier (BAB) and blood–retinal barrier (BRB).

The eye has defense mechanisms that maintain neural homeostasis, protecting visual function and controlling the uptake of substances from the systemic bloodstream. ILM, inner limiting membrane; NFL, nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; OLM, outer limiting membrane; PL, photoreceptor layer; RPE, retinal pigment epithelium.

Figure 2. Currently available DDS formulations.

Eye drops are the easiest DDS formulation; however, achieving an effective concentration is challenging. Intravitreal administration is associated with infection risk. Nondegradable sustained-release formulations provide long-term stable, sustained release but require surgical removal of the DDS. Biodegradable polymeric sustained-release formulations do not require removal but have the disadvantage of a short release period.

Figure 3. Future DDS formulations.

Since it is difficult to keep sustained-release drugs in the eye for long periods of time, reinjection or extraocular implantable devices may be advantageous. Several drugs are being evaluated in clinical trials. In addition, targeted drug delivery via the systemic administration of targeted molecules, such as cellular encapsulation and active targeting, will be established as a future therapeutic strategy.

Figure 4. Gene transfer using Adeno-associated viral vectors.

Adeno-associated viral vectors carrying genes encoding anti-VEGF drug proteins are effective molecularly targeted drugs. After intravitreal administration or subretinal injection, the virus-infected cells continuously produce the protein, thereby enabling long-term VEGF inhibition.

Declaration of Conflicting Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

None

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