



Point-of-Care Nanoplat­forms for Glaucoma and Age-Related Macular Degeneration: Clinical Implications and Emerging Concepts

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Abstract

This chapter focuses on current updates in the development of nanotechnology-based systems for the therapy of ocular disease. The aim of this chapter is to provide the perspective of nanotechnology and existing challenges in conditions of glaucoma and age-related macular degeneration (AMD) with deeper insights into clinical aspects and pathophysiological mechanisms. Topical drug delivery has been quite challenging for the ocular conditions especially in wet AMD, which mostly require intravitreal injections owing to the tear layer and the anatomy of the ocular surface. Sustained ocular therapies to

both anterior and posterior segments of the eye have been made possible only with the significant contribution of nanotechnology. Nanotechnology-driven platforms (nanoscale formulations and smart coatings) offer just a minute fraction of nanotech's potential by plummeting the requirement for intravitreal injections and may lead to hassle-free therapeutic management of ophthalmic conditions like glaucoma and AMD. The intent behind this compilation of literature was to warrant the advances in basic and clinical research in ophthalmology, which may foster better understanding of the disease physiology by providing the impetus for better design and development of dosage forms for intractable ocular diseases such as glaucoma and AMD. Therefore, a comprehensive analysis of the impact of nanomedicine in pathological conditions like glaucoma and AMD has been undertaken in the present study to ensure better disease prevention, new diagnostic procedures, and novel drug treatments whose final endpoint may be preclinical or clinical testing.

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Keywords

Glaucoma · Age-related wet macular degeneration (AMD) · Nanotechnology · Ocular drug delivery · Intraocular pressure (IOP)

11.1 The Nano-State: Impact of Nanomedicine on Ocular Drug Delivery

It is no wonder these days why the “small” matters in pharmaceutical science. With the advent of nanotechnology, the fabrication of nanosystems has emerged as an effective tool to overcome the obstacles in the therapeutic management of ocular diseases and has reshaped the science of ophthalmology. The application of emerging nanotechnological strategies and nanoscience methods has been increasingly adopted for the management of ocular diseases by improving the drug delivery design (bioadhesive enhancement, sustainable release, stealth function, specifically targeted delivery, and stimuli-responsive release) and targeted approaches to both anterior and posterior segments of the eye (Weng et al. 2017). Nanotechnology-driven systems have the ability to deliver both ocular drugs (imagine prescribing eye drops to treat wet AMD) and delivering genes to the retina (in patients with retinitis pigmentosa) or eye tissue via corneal absorption, periocular injection, and intravitreal injection, for ocular disease therapy and diagnosis.

Advances have been carried out for encapsulating conventional drugs in order to broaden the treatment spectrum in ocular clinical settings by increasing bioavailability, decreasing toxicity, and better tissue adherence of the nanocarriers. Further, it is a well-debated argument that the majority of the preclinical studies in the ocular segment are highly focused on the drug targeting and therapeutic efficacy; however, it is warranted that more impetus should be laid on the biodistribution and fate of the nanocarriers as well as clearance from the ocular tissues.

11.2 Challenges in the Ocular Drug Delivery

Despite the enormous insufficiencies, the mainstay option of ocular therapy is a topical application on the ocular surface, which accounts for >90% of ophthalmic preparations in the global markets. Figure 11.1 highlights the anatomy of

the eye, its protective mechanisms, and elimination processes such as tear turnover, nasolacrimal drainage, protein binding, systemic absorption, enzymatic degradation, and complex ocular barriers (corneal barrier, blood–aqueous barrier, and blood–retinal barrier) which pose major obstacles for the ineffective ocular drug delivery.

Further, the administration of any dosage form via topical mode occurs through anatomical (corneal or non-corneal routes) and physiological barriers (such as tear film). The cornea is a very tightly multilayered tissue in which corneal epithelium acts as a principal barrier due to the formation of high paracellular resistance by tight junctions. However, the other layers of the cornea (such as Bowman’s membrane, stroma, Descemet’s membrane, and endothelium) are more permeable to hydrophilic molecules (Sridhar 2018). Non-corneal route circumvents the cornea and encompasses movement across layers—conjunctiva and sclera, which are more suited for the permeation of large hydrophilic molecules (as these layers exhibit low expression of tight junction proteins with respect to corneal epithelium).

Furthermore, topical delivery to cornea becomes herculean task when it influences another physiological barrier, i.e., aqueous layer of the tear film, which rapidly washes away anything in an aqueous formulation, whereas mucus layer with sticky molecules (glycosylated mucins) arrests any foreign particles or pathogens progressing toward cornea, binds them, and prepares for its removal (Hodges and Dartt 2013). In the same way, the blood ocular barrier prevents systemically administered drugs from effective penetration. Further, topical application to the retina is totally ineffective; however, scientists have experimented with alternate modes of drug delivery that can overcome anatomical and physiological barriers presented by conventional routes. These include injections (such as intravitreal (commonly used in wet AMD) subconjunctival, retrobulbar and peribulbar, sub-tendon, and intracameral) through visible portions of the sclera targeting various sections of ocular structures by a trained specialist (Kwatra and Mitra 2013; Mandal et al. 2018).

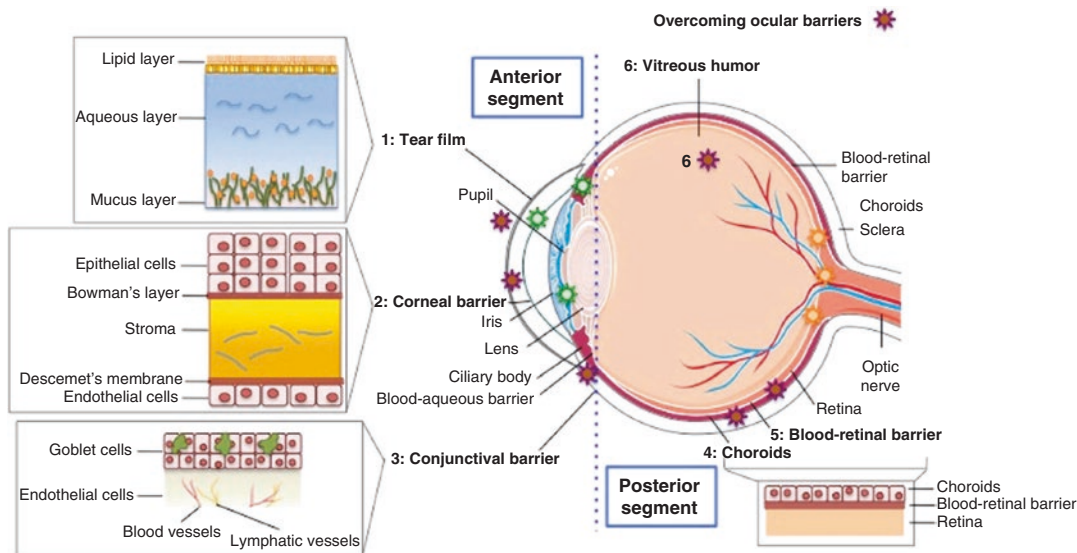


Fig. 11.1 Eye anatomy and various protective mechanisms, elimination processes, and ocular barriers. (Reproduced in original from with licenced permission from Elsevier)

Recently in 2019, Ozkan and Willcox elucidated the significant immunomodulatory role of ocular surface microbiota (low diversity microbiome) and its compositional changes in various ocular surface disorders such as blepharitis, trachoma, and dry eye. The study also revealed the role of the ocular and non-ocular microbiome in retinal diseases including AMD, glaucoma, uveitis, and diabetic retinopathy (Ozkan and Willcox 2019). Therefore, the key challenges of conventional drug delivery systems comprise of multiple drug administrations, dependency on caregivers for drug administration especially in pediatrics and geriatrics, patient-dependent dose precision, physiological barriers, poor bioavailability due to low corneal permeability, and drugs with shorter half-lives. Further, these challenges (such as the role of ocular microbiome in eye homeostasis) and requirements vary tremendously for the anterior and posterior ocular segments.

Nanotechnological approaches have provided a platform, not only to encase the existing drugs employing nanocarriers, they have also given a huge impetus in the efficient delivery of the next generation of medicine especially in ocular diseases. Nanosystems such as nanoparticles, nanocrystals, nanodiamonds, liposomes, dendrimers,

nanoemulsions, and nanodevices (including nanoparticle composed contact lenses) have been developed to provide better tissue adherence, targeted drug release, noninvasive routes of administration with high patient compliance, higher solubility and bioavailability profiles, controlled rate of drug delivery, longer shelf life and duration of action, biocompatibility, biodegradability, stability, and minimal tissue toxicity as depicted in Fig. 11.2.

Hence, it can be postulated that nanoparticle based topical systems (eye drops/solutions) shall be able to penetrate through protective mucins in the tear film, into ocular surface tissue, via cornea into the anterior chamber. These systems also possess capacity of gene delivery and delivery of therapeutically active biomolecules to the posterior segment with enhanced residence time. Moreover, significant progress has been made in the field of nanomedicine to improve the efficiency of anti-glaucoma medications. Nanofabrication systems such as microelectromechanical systems have overcome the limitations of nanodevices and tissue regeneration vesicles for developing glaucoma treatments independent of intraocular pressure (IOP) management based approaches (Cetinel and Montemagno 2016). The first commercial oph-

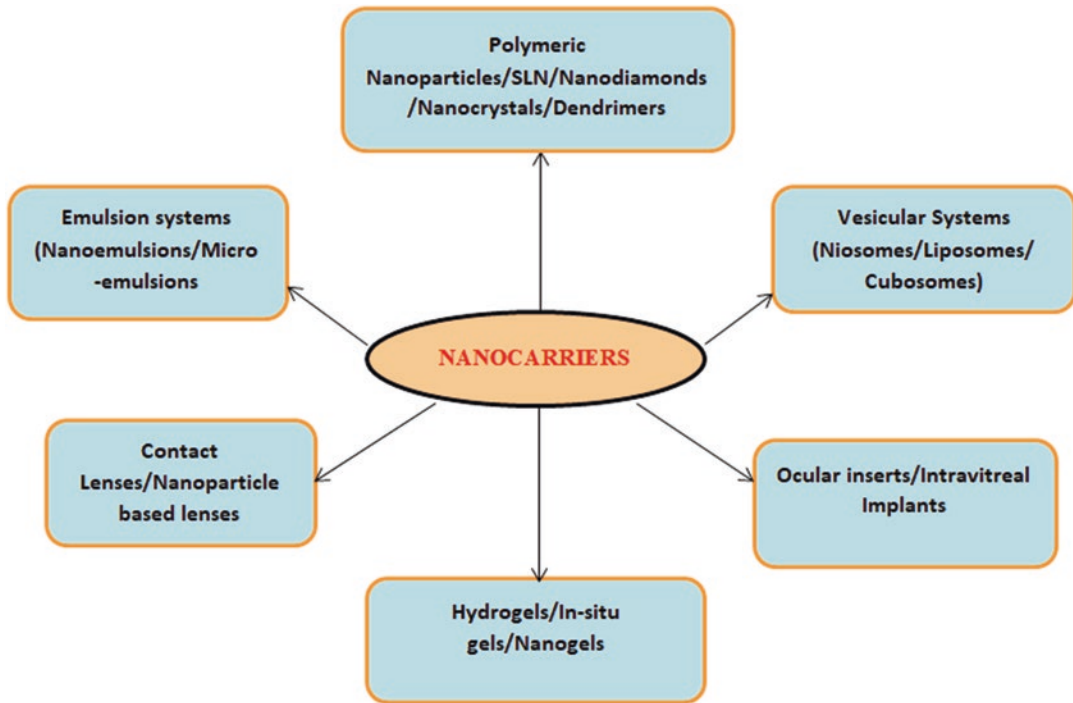


Fig. 11.2 Various novel nanocarriers for ocular drug delivery

thalmic preservative-free anionic nanoemulsion (trade name—Restasis® containing 0.05% cyclosporin A) was developed in early 2000 and approved by US FDA in 2002 for a dry eye condition. Another topical nanoemulsion was marketed as Cyclokat® based on Novasorb® technology by Santen Pharmaceutical Co. Ltd. Further, a drug delivery ophthalmic platform named “Durasite” based on biodegradable polymer polycarbophil has also been commercialized for the condition bacterial conjunctivitis (pink eye). Since then numerous nanotechnologies and drug delivery platforms for ocular conditions related to anterior and posterior eye have been successfully marketed.

tions, and traumas of various types, inflammatory reactions, hereditary disorders, and cataracts. The conventional drugs and formulations which are fabricated for the major diseases related to anterior chamber (i.e., dry eye, keratitis, conjunctivitis, and cataract) primarily suffer from poor bioavailability because of corneal barrier and precorneal factors. Studies have revealed that conventional systems such as eye drops may cause damage to the corneal surface, film instability, and inflammation (Chung et al. 2016). Figure 11.3 illustrates the major disease burden to both the segments of the eye.

11.3 Emerging Ocular Manifestations Related to Anterior Segment of the Eye

Disorders of the anterior segment of the eye are the leading causes of ocular morbidity. Such conditions include dry eye conditions, infec-

11.4 Emerging Ocular Manifestations Related to the Posterior Segment of the Eye

In contrast to diseases of the anterior eye, diseases related to posterior segment occur most commonly in the retina and choroid.

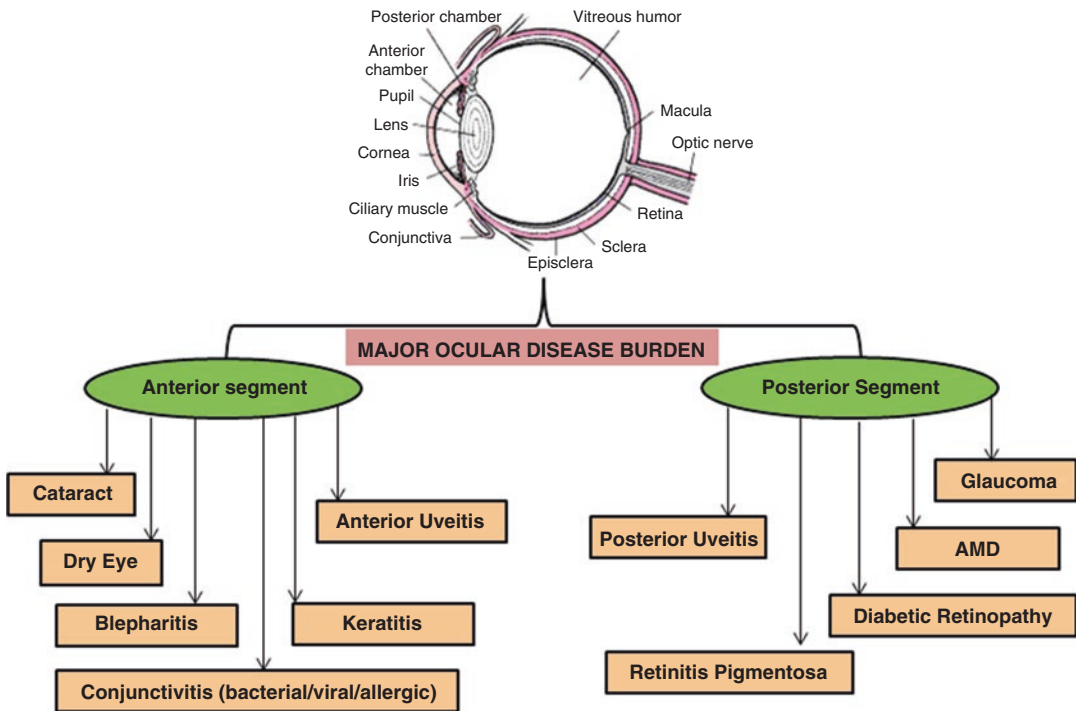


Fig. 11.3 Major disease burden to both segments of the eye

11.4.1 Glaucoma

11.4.1.1 History and Prevalence

The use of the term “glaucoma” (*glaukos* means bluish gray) first featured in Aphorisms of Hippocrates (460–375 BC) primarily due to characteristic color assumed by the anterior segment of the eye and not due to depiction of any disease form. The term was largely misinterpreted with cataract until the characteristic features of the disease appeared in the first English book of ophthalmology by Richard Banister.

As far as prevalence is concerned, glaucoma is the second leading cause of irreversible vision loss worldwide. According to the World Health Organization (WHO) statistics, it is responsible for blindness to >12% of patients (approx. 4.5 million cases) globally. Further, the projections indicate that approximately 79.6 million people will be affected by glaucoma by 2020 (Tham et al. 2014). Some of the potential risk factors which may lead to glaucoma are as follows:

- Age > 40 years
- African, Hispanic, or Asian heritage
- Family history of glaucoma
- Myopic/poor vision
- Diabetes, migraines, high blood pressure, and poor blood circulation
- High eye pressure
- Chronic use of steroids
- Injury/trauma to the eye
- Corneas that are thin in the center
- Thinning of the optic nerve

11.4.1.2 Pathobiogenesis and Mechanism

This multifactorial disorder is primarily a group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells (central nervous system (CNS) neurons having their cell bodies in the inner retina and axons in the optic nerve). The pathological progression of the disease in the inner retina is indicated by degeneration of the optic nerve head termed as “cup-

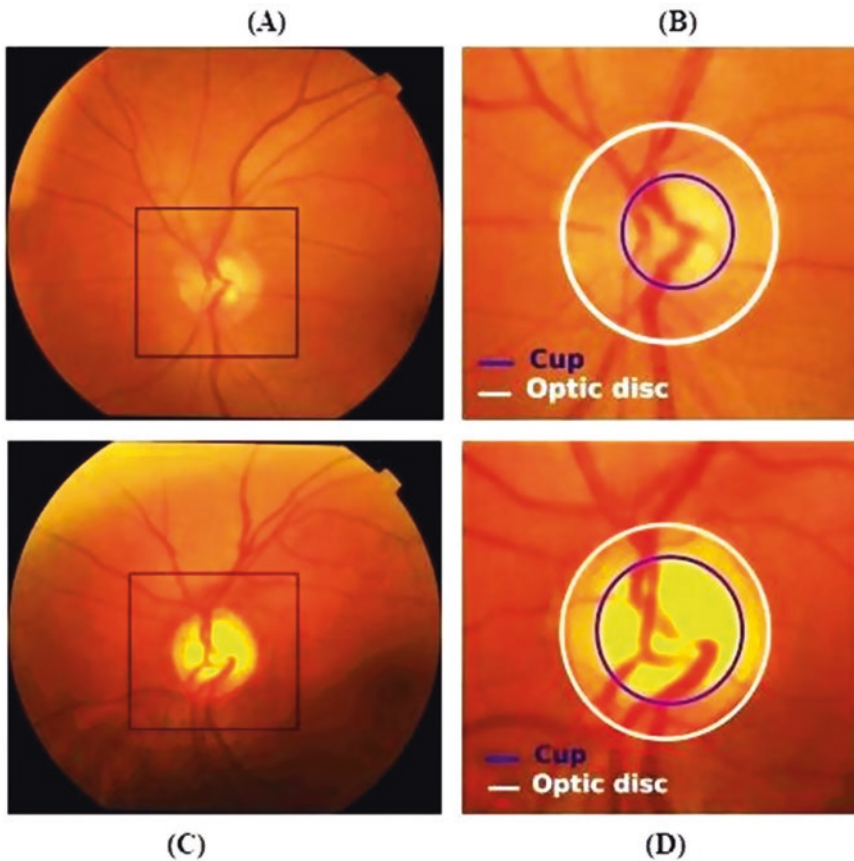


Fig. 11.4 Schematic illustration of regions: (a) healthy retina, (b) normal optic disc regions of retina, (c) glaucomatous retina, and (d) optic disc and optic cup regions of

retina with neurodegenerative changes associated in glaucoma and relatively high CDR. (Reused in original form with licenced permission from Elsevier)

ping of optic disc” (neuroretinal rim thinning, and sectoral retinal nerve fiber layer thinning) (Chang and Goldberg 2012; Lee et al. 2019). Figure 11.4 depicts the schematic view of healthy state of retina (Fig. 11.4a) along with normal optic cup and disc regions of retina (Fig. 11.4b) in comparison to glaucomatous retina (Fig. 11.4c) along with neurodegenerative disease progression possessing relative high cup/disc ratio (CDR) (Fig. 11.4d). This neurodegenerative progression transpires owing to abnormally high IOP, ocular blood flow, oxidative stress, decreased axoplasmic flow, and genetic predisposition which may be asymptomatic in the earlier stages (a primary reason for the frequently delayed diagnosis) (Weinreb et al. 2014). However, dur-

ing the late stages of the disease, progressions of neuronal loss include the lateral geniculate nucleus and the visual cortex. Figure 11.5 summarizes the cascade of the events involved in the pathobiogenesis of glaucoma and the management strategies (based on IOP-dependent and non-IOP-dependent approaches) to resolve the ocular condition. The normal range of IOP is 2–22 mm Hg, whereas eye pressure of greater than 22 mm Hg is considered higher than normal. When the IOP is greater than 22 mm Hg without any symptom, the condition is termed as state of ocular hypertension, and the person with high IOP is referred to as “*glaucoma suspect*”. This term may also be used in case of suspicious optic nerve or with strong family history of glaucoma.

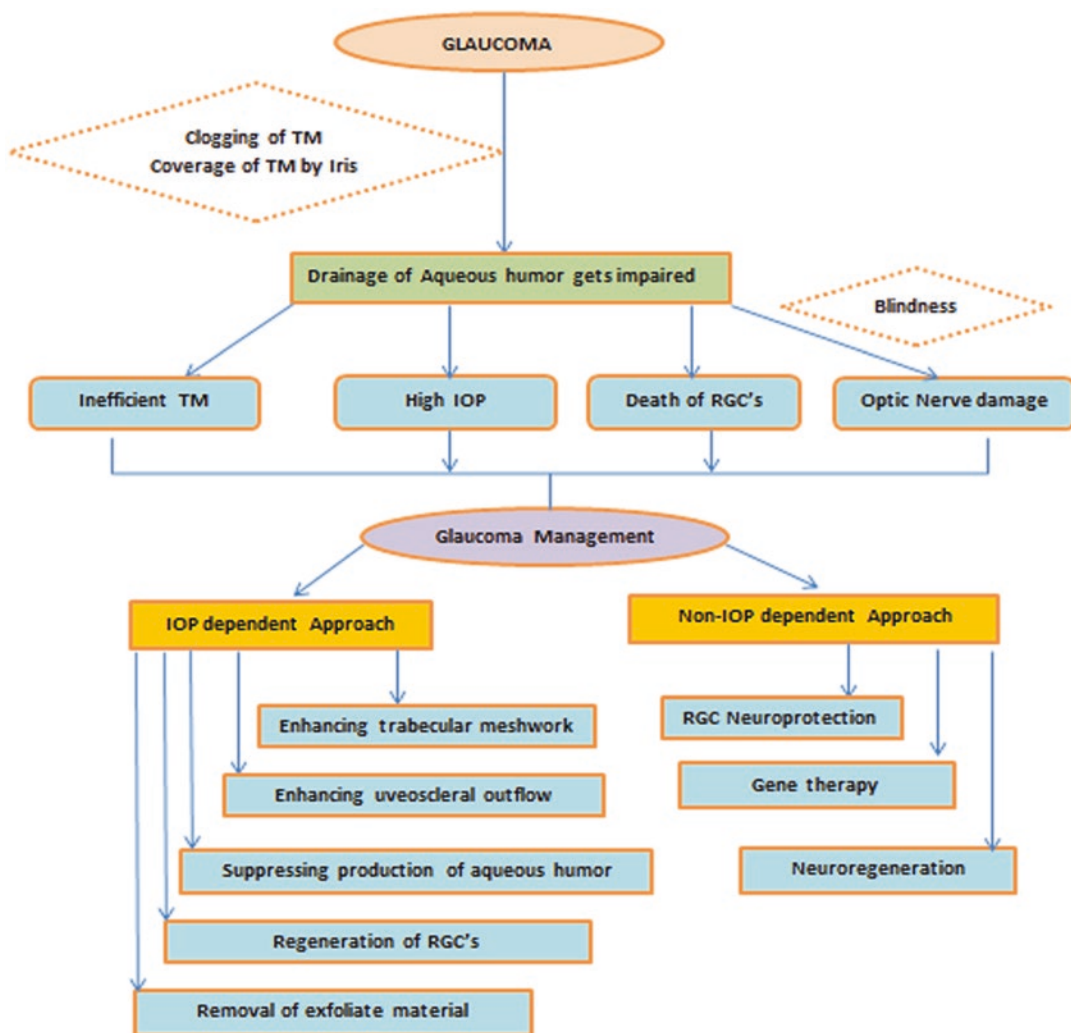


Fig. 11.5 Schematic representation of pathogenesis and management of glaucoma

The vertical cup/disc ratio (CDR) for normal individuals is 0.3 which is used for the assessment of the glaucoma suspect, as cup size is related physiologically to disc size and pathologically to glaucomatous damage. Further, IOP compensation is also highly indispensable for maintaining the physiological homeostasis of the eye. A significant quantitative relationship for IOP determination is

$$IOP = F / C + PV$$

(where *F* denotes for aqueous fluid formation rate, *C* is outflow rate, and *PV* is episcleral venous pressure). Although the elevated IOP is one of the

prime causes for glaucoma, however, it is not the only contributory factor for glaucoma. Further, exfoliation syndrome also causes glaucoma due to defects in the microfibrils, which alter the biomechanical properties of surrounding tissue and affect the signaling. The biological mechanism of glaucoma has not been still fully elucidated, and several key factors (such as mechanical compression, ischemia, oxidative stress, neurotrophic growth factor deprivation, intracellular calcium toxicity, activation of autoimmunity, and glutamate neurotoxicity) play a significant role in its progression, which are yet under investigation (Tian et al. 2015).

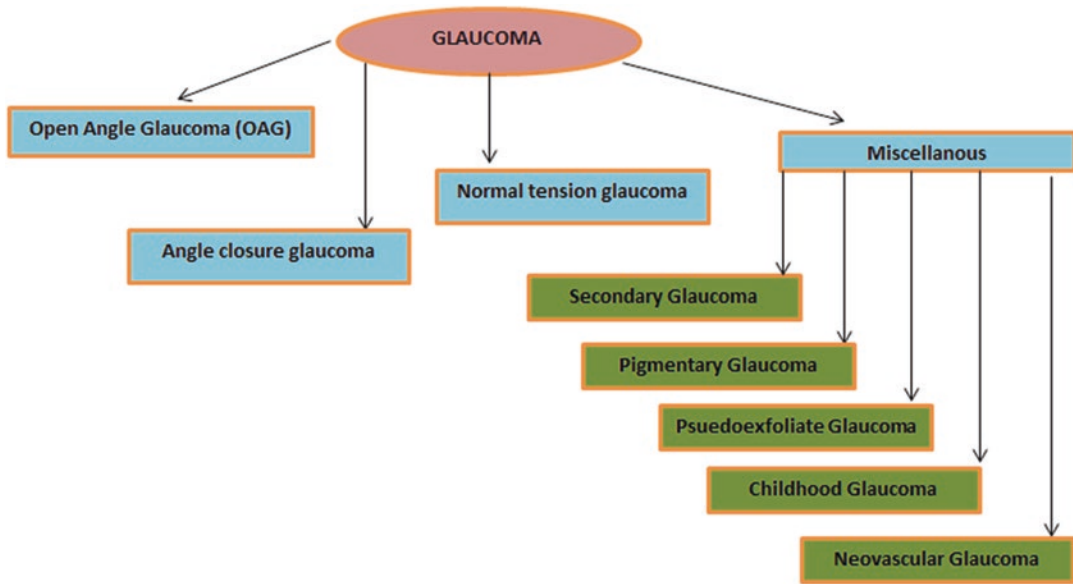


Fig. 11.6 Classification of glaucoma

In the literature, glaucoma is commonly classified into primary and secondary based on the anatomy of the anterior chamber and the drainage pathway (open and narrow angles). However, on the basis of combined pathologies including comorbid conditions (i.e., infection, mechanical injury, or neovascularization that often affect a single eye alone), it may be best classified as shown in Fig. 11.6.

Open-angle glaucoma (OAG) or wide-angle glaucoma (WAG) is the primary form of the disease with 80% rate of incidence and occurs due to inadequate drainage in front of the eye. Figure 11.7 represents the anatomical representation of primary OAG, which is characterized by the abnormal elevated IOP levels transmitted from anterior segment to posterior segment of globe containing retina and optical disc (where retinal ganglion cells (RGCs) and axons reside) (Fig 11.7a). In aqueous outflow pathways, the entrance to the drainage canals remains clear, but congestion occurs inside the drainage canals (the drain space between iris and cornea becomes too narrow), which results in aqueous humor accumulation leading to abnormal IOP (Fig 11.7b). Thus, the occurrence of primary OAG is primarily characterized by elevated IOPs or signifi-

cantly low IOPs (known as normal-tension glaucoma, which affects 40% of glaucoma patients and results in visual loss).

The secondary type is angle-closure glaucoma (ACG) or narrow-angle glaucoma (NAG) in which IOP elevates due to coverage or congestion of drainage angle. Secondary glaucoma provides the most convincing evidence that elevated IOP may cause optic nerve damage. Sometimes, an acute attack of glaucoma may occur having any of such symptoms such as blurredness, eye pain, headache, nausea, and vomiting.

The causative factors for the congestion of drainage angle could be trauma, certain medications such as corticosteroids, inflammation, tumor, or conditions such as pigment dispersion or pseudo-exfoliation.

11.4.2 Conventional Therapies (IOP-Dependent Approaches)

Among the non-invasive applications, topical administration of eye drops, eye lotions, and solutions is still widely preferred to maintain the aqueous humor production, IOP, facilitate tra-

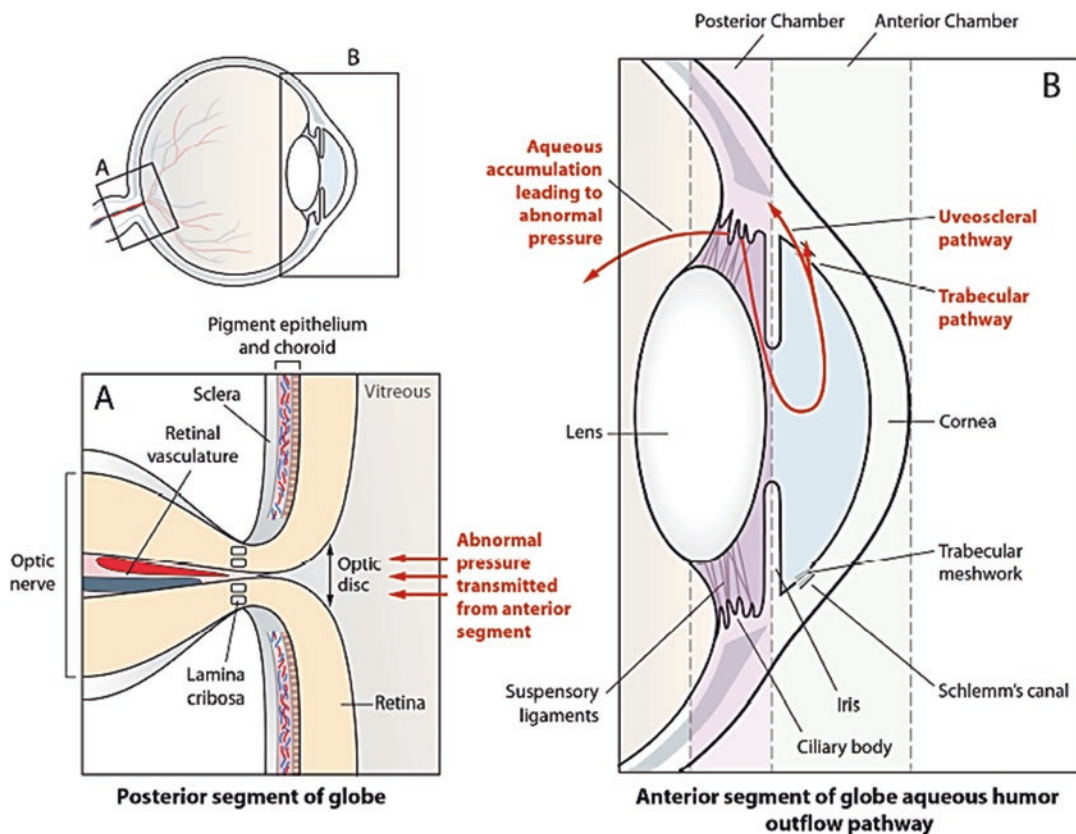


Fig. 11.7 Schematic anatomical representation of primary form of open-angle glaucoma: (a) abnormal elevated IOP levels transmitted from anterior segment to posterior segment of globe containing retina and optical

disc; (b) aqueous outflow pathways from anterior segment. (Reused in original form with licenced permission from Elsevier)

becular meshwork (TM), and enhance uveoscleral outflow. Table 11.1 summarizes the top-listed (based on IOP-dependent approaches involving maintenance of IOP) ocular products approved by US FDA during the last decade in chronological order, which is currently under clinical use for glaucoma treatment.

To date, there are numerous drugs that control IOP, which are most commonly used as a topical solution applied to the eye (eye drops)—a convenient noninvasive method of administration. These topical drugs (which primarily act to decrease the production of aqueous humor and facilitate drainage through the TM, increasing uveoscleral out-

flow) majorly belong to five categories: β -blockers, carbonic anhydrase inhibitors, prostaglandin analogs, sympathomimetic drugs, and parasympathomimetic drugs as shown in Table 11.2.

In addition, some fixed combination therapies have also been approved by US FDA for effective IOP control when the patient does not respond to one pure form of medication. Some of the fixed combination therapies for glaucoma mainly include prostaglandin analogs/ β -blockers, carbonic anhydrase inhibitors/ β -blockers, and α 2-adrenergic agonists/ β -blockers and carbonic anhydrase inhibitors/ α 2-adrenergic agonists.

Table 11.1 Top-listed US FDA approved products for glaucoma during the last decade in chronological order

Ocular Condition	Formulation	Trade name/ company	Active agent/mechanism of action	Therapeutic indication	Approved year
Glaucoma	Eye solution (drops)	Rocklatan (Aerie Pharmaceuticals)	Netarsudil and latanoprost	Elevated IOP in OAG or ocular hypertension	March 2019
		Vyzulta (Bausch & Lomb)	Latanoprostene (nitric oxide-donating prostaglandin F2-alpha analog)	Elevated IOP in OAG or ocular hypertension	November 2017
		Rhopressa (Aerie Pharmaceuticals)	Netarsudil (Rho kinase inhibitor)	Glaucoma or ocular hypertension	December 2017
		Zioptan (Merck)	Tafluprost (fluorinated analog of prostaglandin F2a)	Elevated IOP	February 2012
		Lumigan (Allergan)	Bimatoprost	Reduction of IOP in open-angle glaucoma or ocular hypertension	March 2001
		Travatan (Alcon)	Travoprost	Reduction of elevated IOP in OAG or ocular hypertension	March 2001
		Cosopt (Merck)	Dorzolamide hydrochloride and timolol maleate (combination of a topical carbonic anhydrase inhibitor + beta-adrenergic receptor blocker)	Glaucoma or ocular hypertension	April 1998
Ophthalmic suspension or drops	Betaxon (Alcon)	Levobetaxolol hydrochloride (beta-adrenergic antagonist)	Lowering IOP in chronic OAG or ocular hypertension	February 2000	
Ophthalmic solution	Rescula (Ciba Vision)	Unoprostone isopropyl	OAG or ocular hypertension	August 2000	
Ophthalmic Solution	Alphagan (Allergan)	Brimonidine	OAG and ocular hypertension	September 1996	

11.4.3 Novel Therapies (Non-IOP-Dependent Approaches)

There is a wide acceptance among the clinicians and technologists that management of glaucoma based on IOP-dependent approaches only is not sufficient enough to provide comprehensive treatment of the disease. Thus, more attention has been focused on non-IOP-based approaches which include neuroprotectives and neurodegenerative procedures to preserve neuronal structure and function. Another view is the combination of IOP (use of IOP-lowering drugs) and non-IOP approaches (neurotrophic

factors and antioxidants) simultaneously for effective management of glaucoma (Nafissi and Foldvari 2015).

11.4.3.1 Neurotrophic Factor (NTF)

With the advent of genome engineering and the profound understanding of the mechanism of neurodegenerative disorders related to ocular diseases such as glaucoma, novel gene therapies such as neurotrophic factor (NTF), cell replacement, and therapeutics have shown the potential to become the new ray of hope for the patient's nonresponsive IOP-dependent approaches.

Table 11.2 Classification of commercial proprietary drugs available in the market with historical timeline of treatment options for the management of glaucoma

Class of drugs/methods currently used in glaucoma	Timeline of drugs introduced for IOP reduction in glaucoma
Sympathomimetic drugs —Brimonidine (<i>Alphagan, Alphagan-p, Bimonidintartrat, Brimoratio, Glauclin</i>); apraclonidine (<i>Iopidine</i>); dipivefrin (<i>Propine</i>); epinephrine (<i>Glaucon, Epifrin</i>)	Pilocarpine—1875 Epinephrine—1925 Diamox—1956
Parasympathomimetic drugs —Pilocarpine (<i>Pilokarpin, Isopto Carpine, pilocar, Pilopine HS</i>); echothiophate (<i>Phospholine Iodide</i>)	Timolol—1978 Pilocarpine/timolol—1992
Beta-blockers —Timolol (<i>Optimol, Timacar Depot, Timoptol-LA, Timolol, Nyogel L.P., Timogel, Timosan, Aquanil</i>); levobunolol; carteolol (<i>Ocupress</i>); metipranolol (<i>OptiPranolol</i>); betaxoxol (<i>Betoptic</i>); nipradilol	Dorzolamide—1994 Latanoprost and brimonidine—1996
Carbonic anhydrase inhibitors —Dorzolamide (<i>Trusopt, Arzolahamid, Dorzolamid</i>); brinzolamide (<i>Azopt</i>); acetazolamide (<i>Diamox</i>); methazolamide (<i>Neptazane</i>)	Brinzolamide and dorzolamide/timolol—1998 Bimatoprost—2000
Prostaglandin analogs —Tafluprost (<i>Taflutan, Saflutan, Zioptan</i>); latanoprost (<i>Xalatan, Monoprost, Latanoprost</i>); bimatoprost (<i>Lumigan</i>); travoprost (<i>Travatan</i>); unoprostone isopropyl (<i>Rescula</i>)	Travoprost and latanoprost/timolol—2001 Brimonidine/timolol—2005 Bimatoprost/timolol and travoprost/timolol—2006 Tafluprost—2008 Brinzolamide/timolol—2009 Monoprost—2013 Brimonidine/brinzolamide and tafluprost/timolol—2014
Surgery —Laser trabeculoplasty; iridotomy	

Recently in August 2018, US FDA has approved an ophthalmic product (trade name—*Oxervate*®, by *Dompe*), a novel recombinant human nerve growth factor (rhNGF; structurally similar to NGF protein synthesized in the body including ocular tissues), for neurotrophic keratitis (which causes corneal scarring and vision loss).

NTF belongs to a group of proteins secreted by the central and peripheral nervous system which are critical for its role in neuroprotection during glaucoma. The various NTF's nerve growth factor (NGF) family members such as glial cell derived neurotrophic factor (GDNF), brain derived neurotrophic factor (BDNF), and cerebral dopamine neurotrophic factor (CDTF) have been the subject of comprehensive investigation and have shown experimentally immense application for the long-term effective management of glaucoma (Kimura et al. 2016).

Many investigators have vowed for the exogenous supplementation of NTF, apoptotic inhibitors, and survival factors for the regeneration of RGC in glaucoma. Targeted gene therapies for the delivery of transgenes employing viral/nonvi-

ral vectors encoding NTFs have also been studied (Pietrucha-Dutczak et al. 2018). However, direct targeting of NTFs by living cells and direct replacement of growth/survival factors, apoptosis inhibiting factors manipulated genetically ex vivo would be highly beneficial and facilitate long-term expression for sustained neuroprotection. Some authors have revealed the useful application of stem and progenitor cells expressing and secreting NTFs for neuroprotection and long-term expression in preclinical animal models of glaucoma (Johnson et al. 2011; Chamling et al. 2016).

11.4.3.2 Role of DNA Therapeutics

The management of neurodegenerative disorders such as glaucoma employing DNA vectors owing to their small sizes offers a potential substitute to the conventional plasmids for superior biosafety standards, immune and biocompatibility, and improved gene transfer in rapidly dividing cells and tissues with higher regenerative capacity (Khar et al. 2010). Therefore, the gene therapy for glaucoma requires sustained and stable expression of tightly controlled DNA vectors as

most of the DNA vectors become diluted after subsequent mitosis.

11.4.3.3 RGC Survival Therapies

The progression of optic neuropathy in glaucoma is primarily characterized by loss of RGCs and typical visual field defects. Some of the other reasons for RGC death are the reduction in neurotrophic factors owing to local vascular insufficiency at optic nerve head. In some cases, if neuroprotection is overdue because of severe cell loss, RGC replacement therapy could be preferably used in such cases.

With the advent of the concept of neuroprotection, various neuroprotectives have been investigated to minimize the RGC loss and retinal damage. Guo et al. studied the topical application of CoQ10 on RGC apoptosis *in vivo* in a rat model. It was observed that CoQ10 (0.1%) significantly regressed the staurosporine-induced RGC apoptosis with respect to 0.05% CoQ10. The possible mechanism for this apoptosis inhibition could be potentiated by inhibition of mitochondrial depolarization, cytochrome *c* release, and caspase-9 activation (Guo and Cordeiro 2008). In addition to RGC survival, the role of CoQ10 has also been implicated in the IOP-lowering treatment in glaucoma. Another significant neuroprotective agent is citicoline, which promulgates the stimulation of phospholipid synthesis and phosphatidylcholine in the inner mitochondrial membranes. Various investigations have embarked on the basis of experimental evidence which confirms the neuroprotective role of citicoline. In an investigation, Matteucci et al. studied the role of citicoline in terms of apoptosis and caspase activation in retinal cultures (extracted from rat embryos) in a concentration-dependent manner. It was observed that citicoline restricted neuronal cell damage both in glutamate-treated and high glucose-treated retinal cultures by decreasing proapoptotic effects and conflicting synapse loss (Matteucci et al. 2014). Few other investigations have also hypothesized the antiapoptotic effect of citicoline in mitochondria-dependent cell death and axon regeneration (Oshitari et al. 2002;

Park et al. 2005; Schuettauf et al. 2006; Nucci et al. 2018).

11.4.3.4 Gene Therapy

Gene therapy is also another approach for neuroprotection employed to deliver protective or antiapoptotic genes for regeneration and small interference RNA (siRNA) molecules for silencing inhibitory factors in advanced stages of glaucoma (Martínez et al. 2014). Investigations have been carried out to study axon regeneration (or by blocking axonal growth-inhibitory factors such as oligodendrocyte myelin glycoproteins and myelin-associated glycoproteins) using siRNA protein system (Yang and Schnaar 2008; Schnaar and Lopez 2009).

Few approaches such as cell-based regeneration of TM tissue or whole tissue regeneration have been studied as a part of future treatment strategies. TM stem cells have been investigated in terms of their localization into TM and then further differentiated into functionalized TM cells. The replacement therapy using artificial TM tissues with improved cell attachment has also been studied in cultured human TM cells.

11.4.3.5 Role of Nanomedicine in the Management of Glaucoma

Nanotechnology-based treatments show a great deal of promise in overcoming these complications and form the basis for next-generation glaucoma treatment strategies, with the help of applications such as controlled release, targeted delivery, increased bioavailability, diffusion limitations, and biocompatibility. Although topical application in glaucoma still exhibits significant primary and adjunctive role, however, diverse novel strategies have been devised with the application of nanocarriers. During the last two decades, the prime focus of preclinical investigations involving antiglaucomatic nano-drug delivery approaches (as summarized in Table 11.3) has been to revolutionize the mode of drug administration in ocular tissues by improving the precorneal residence time (e.g., formulating sus-

Table 11.3 Summary of preclinical investigations carried out in the last two decades involving nanotechnological platfoms and devices for glaucoma

Nanotechnological platform	Payload	Biomaterial	Clinical stage/Therapeutic indication	Remarks	Reference/Trial no.
Hydrogel	Mitomycin-C	Pluronic F127 loaded thermogel	Preclinical/glaucoma	Hydrogel showed good compatibility and sustained release in intraocular after glaucoma surgery	Xi et al. (2014)
	Timolol maleate (Timoptic-XE®)	Thermogel	Commercially marketed/ glaucoma	Topical treatment for glaucoma	Schenker and Silver (2000)
Contact lenses	Brimonidine	(PLGA-PEG-PLGA) copolymer	Preclinical/glaucoma	Sustained drug release; relief in IOP; good biocompatibility to epithelial cells	Sun et al. (2017)
		Propoxylated glyceryl triacrylate nanoparticles in contact lens		In vivo studies (beagle dogs) with hydrogel lenses (incorporated with timolol-PGT nanoparticles) showed sustained release for one month after an initial burst and a reduction in IOP	Jung et al. (2013)
		Vitamin E-coated narafilcon A lenses		In vivo study showed over 4 days of treatment, significant reduction of IOP in dogs	Peng et al. (2012)
		Unmodified commercial vasurfilcon A, etafilcon A, and vifilcon		In vivo study showed no toxicity after 2 weeks, IOP levels decreased to similar to daily eye-drop therapy	Schultz et al. (2009)
		MAA molecularly imprinted pHEMA gels		In vitro study showed enhanced loading and pH-dependent hydrogel swelling for drug release	Alvarez-Lorenzo et al. (2002)
		Vitamin E-coated senofilcon-A lenses		Treatment with vitamin E lenses demonstrated a prolonged IOP-lowering effect compared to eye drop	Hsu et al. (2015)
Nano-ophthalmic injection	Latanoprost	Senofilcon-A (ACUVUE®)		In vivo studies showed that drug-polymer contact lenses films provided an initial burst in the aqueous humor followed by a steady-state concentration comparable to the concentration of marketed eye drops	Ciolino et al. (2014)
	Acetazolamide and ethoxzolamide	Poly(2-hydroxyethyl methacrylate) (pHEMA)		pHEMA hydrogels loaded contact lens were highly cytocompatible, better drug release and possessed good oxygen permeability	Ribeiro et al. (2011)
	Puerarin	Poly(2-hydroxyethyl methacrylate-co-N vinylpyrrolidone-co-methyl acrylate) (pHEMA-NVP-MA)		Contact lenses extended the mean resident time of puerarin to 77.45 min from 12.88 min of 1% puerarin eye drops and exhibited similar bioavailability with puerarin eye drops in tear fluid	Xu et al. (2010)
	Latanoprost	Controlled release patented liposomes (with size of 100 nm) for subconjunctival injection	Phase II/glaucoma	POLAT-001® (controlled release liposomal injection sponsored by Peregrine Ophthalmic Pvt. Ltd., Singapore) compared with latanoprost eye solution for reduction of mean IOP from 28 mm Hg to 15 mm Hg in an open labeled study on 6 patients	NCT02466399

(continued)

Table 11.3 (continued)

Nanotechnological platform	Payload	Biomaterial	Clinical stage/Therapeutic indication	Remarks	Reference/Trial no.
Nanoparticles	Curcumin	Pluronic-F127 stabilized D- α -tocopherol polyethylene glycol 1000 succinate	Preclinical/neuroprotective therapy in glaucoma	Neuroprotection against glutamate and CoCl ₂ – induced injury in retinal cultures in vitro and significantly preserved RGC density in rodent models of ocular injury	Davis et al. (2018)
	Brimonidine	Chitosan methylcellulose (gelling agent)	Preclinical/glaucoma	Nanoparticles incorporated gel showed sustained release and sustained IOP reduction (>25 h) compared to eye drops	Ibrahim et al. (2015)
Dorzolamide HCl	Dorzolamide HCl	Chitosan and sodium alginate	Preclinical/neuroprotective therapy in glaucoma	Nanoparticles showed sustained release and slower corneal permeation compared to commercial eye drops in rabbits	Katiyar et al. (2014)
		Poly (lactide-co-glycolide)		Enhanced corneal permeation w.r.t. Trusopt® and higher drug concentration in aqueous humor with IOP reduction	Warsi et al. (2014)
		6-O-Carboxymethyl chitosan		Showed sustained drug release, and in vivo studies revealed non-irritant particles with prolonged antiglaucoma effect	Shinde et al. (2013)
Cationic solid lipid nanoparticles (SLNs)	Betaxolol HCl	Chitosan	Preclinical/neuroprotective therapy in glaucoma	Nanoparticles exhibited sustained release up to 12 h and significant IOP reduction reaching a peak of 9.9 ± 0.5 mmHg, compared to control after 5 h.	Jain et al. (2013)
		Melatonin		Showed enhanced ocular retention time, and effective in IOP reduction for 24 h	Kouchak et al. (2016)
Modified SLNs	Methazolamide	GMS (solid lipid) and lecithin	Preclinical/neuroprotective therapy in glaucoma	Chitosan modified SLNs exhibited prolonged in vitro release, better corneal permeation and better reduction in IOP than unmodified SLN and marketed eye drops	Yu et al. (2015)
		SLNs		SLNs exhibited sustained release and significant IOP reduction compared to marketed eye drops	Leonardi et al. (2015)
SLN and nanolipid carriers	Dorzolamide	GMS (solid lipid) phospholipid-S100	Preclinical/neuroprotective therapy in glaucoma	Both SLNs and NLCs (after autoclaving) were non-irritant to ocular mucosa and exhibited high entrapment compared to non-autoclaved ones	Mehner and Mäder (2001)
		GMS (solid lipid) Castor oil (liquid lipid)		The optimized formulation showed reduction of IOP by 8.3 mm Hg within 3 h and was maintained for 12 h	Wang et al. (2014)
Cationic nanostructured lipid matrix	Dorzolamide	Compritrol® 888 ATO cetostearyl alcohol stearylamine	Preclinical/neuroprotective therapy in glaucoma	Dorzolamide-based formulation caused IOP reduction with significant RGC protection	Pitha et al. (2018)
Microparticles	Dorzolamide	Poly(ethylene glycol)-co-poly (sebacic acid) (PEG3-PSA)	Preclinical/neuroprotective therapy in glaucoma		

		Preclinical/glaucoma			
Nanosheets	Latanoprost	Chitosan and sodium alginate		One day application of LP loaded NS (on cornea) significantly reduced IOP in rats (sustained effect for 7 days)	Kashiwagi et al. (2013)
Nanoliposomal carrier		Egg phosphatidylcholine		Sustained release for subconjunctival injection; successful preclinical study on rabbit and monkey	Natarajan et al. (2012) and NCT01987323
Liposomes	Pilocarpine HCl	Dipalmitoyl phosphatidylcholine		Showed reduced IOP in glaucomatous pigmented rabbits	Moneim et al. (2000)
Unilamellar liposomes	Diltiazem HCl	Soyaphosphatidyl choline and cholesterol		Vesicles, rigidified using cholesterol showed high entrapment efficiency, prolonged release and high reduction in IOP activity in rabbits w.r.t solution	Mokhtar Ibrahim et al. (2014)
Small unilamellar liposomes	Brimonidine tartrate	Cholesterol DPPC (1,2 dipalmitoyl-sn-glycero-3-phosphocholine)		Liposomes showed prolonged release of drug, and IOP reducing activity in normotensive rabbits was sustained for a longer period of time than drug solution	Prabhu et al. (2010)
Large unilamellar liposomes	Latanoprost	Egg phosphatidylcholine		Exhibited sustained in vitro release for 2 weeks; subconjunctival injection of liposomes maintained a sustained IOP-lowering effect in rabbits w.r.t topical daily administration	Natarajan et al. (2012)
Liposomal gels		Phospholipon® 90G, cholesterol, and Pluronic® F127 (gelling agent)		Liposomes vesicles with enhanced entrapment efficiency were incorporated Pluronic® F127 gels for sustained drug release (~45% in 48 h) and maintained IOP reduction for 72 h w.r.t marketed eye drops	Fathalla et al. (2015)
Liposomes	Brinzolamide	Soybean phosphatidylcholine (S100), cholesterol		Liposomes showed 6.2-fold increase in the corneal permeability and sustained IOP reduction in rabbits compared to commercial suspension	Li et al. (2016)
Nanoliposomes	Dorzolamide HCl	Phospholipon 85G® cholesterol		Liposomes showed enhanced transcorneal permeation compared to dorzolamide solution and greater IOP reduction compared to marketed eye drops	Kouchak et al. (2016)
Liposome in ion-sensitive in situ gel	Timolol maleate	Soybean phosphatidylcholine, cholesterol, and deacetylated gellan gum (gelling agent)		Liposomes in situ gel revealed a corneal retention time superior to commercial eye drops and to liposomes and were non-irritant to ocular tissues and showed fast IOP reduction compared to eye drops	Yu et al. (2015)
Nanofiber patch	Timolol maleate Dorzolamide HCl	Polyvinyl alcohol and polycaprolactone		The patch possessed very high mucoadhesive strength and retained for a longer period in the eyes (maintained IOP for 72 h)	Gagandeep et al. (2014)
Nanofilms	Timolol maleate	Chitosan		In vivo study showed IOP reduction same commercial eye drops in rabbits	Fulgêncio Gde et al. (2012)
Nano-ocular inserts	Brimonidine tartrate	HPMC, SA, Na-CMC		Na-CMC inserts showed significant IOP lowering in normotensive rabbits. SA-based inserts showed a stable IOP-lowering effect for 5 h	Labib et al. (2013)
		PVP K-90, HPMC, Carbopol, SA, Chitosan		Ocular inserts showed superior sustained effect w.r.t plain drug solution and exhibited more IOP-lowering effect compared to its non-coated or dual-side-coated counterpart in albino rabbits	Aburahma and Mahmoud (2011)

pensions and ointments, viscous vehicles, bioadhesive vehicles, and in situ gelling systems), sustained corneal permeation (e.g., pro-drugs, penetration enhancers, ion pairs, iontophoresis, and cyclodextrins), improved tissue adherence (e.g., liposomes, emulsions, nanoparticles, and nanocapsules), ocular biocompatibility (e.g., degradable/non-degradable matrices, collagen shields, nanoparticle embedded contact lenses, drug loaded into performed lenses and membrane-controlled devices), and lowering ocular irritation with improved patient compliance (e.g., implantable devices).

11.4.4 Age-Related Macular Degeneration (AMD)

11.4.4.1 Prevalence

Age-related macular degeneration (AMD), or also known as age-related maculopathy, is one of the most prominent and commonest causes of adult blindness in industrialized nations and people age more than 50 years. Globally, AMD ranks third as a cause of blindness after cataract and glaucoma (WHO, 2019). Approximately, 11 million people in the United States have some form of AMD, and these numbers are expected to double to nearly 22 million by 2050. The statistical projections about AMD indicate that the number of people living with macular degeneration is expected to reach 196 million worldwide by 2020 and increase to 288 million by 2040 (Pennington and DeAngelis 2016).

As per the statistics of Macular Society, UK, nearly 600,000 people are affected by vision loss due to some form of AMD, and around 70,000 new cases are being reported annually (with a rate of 200 cases per day). It has been projected that by 2050, the number of AMD patients will be more than double to 1.3 million. In terms of cost, it is estimated that AMD burdens huge health costs to at least £1.6bn a year. Some of the causative factors which may lead to AMD condition are as follows:

- Obese/overweight population (or patients with high cholesterol)

- Smoking; alcohol consumption
- Age (>50 years)
- Arterial hypertension
- Cardiovascular disease or high cholesterol levels
- Light exposure (UV-A or UV-B rays)
- Low dietary intake of antioxidants, zinc
- Family history (siblings with AMD have four times more chances to get AMD than the no relatives with AMD)

11.4.4.2 The Current Line of Treatment Options

Dry AMD

During the initial phase of dry AMD (or atrophic AMD), oral vitamin supplementation (such as lutein, zeaxanthin, lycopene, or tocopherol or centrophloxine, vitamin C, and beta carotene) and zinc are prescribed in order to ameliorate the lipofuscin accumulation and reduce the symptoms in AMD (Age-Related Eye Disease Study Research Group 2001; Birch and Liang 2007; Khoo et al. 2019). However, patients with advanced dry AMD, also called geographic atrophy (GA), have no effective treatments available to them.

Wet AMD

The pharmacological interventions for wet AMD are based on periocular or intraocular drug administration. These intravitreal injections achieve improved therapeutic concentrations at the target tissues; however, the rapid clearance of these agents is still a big challenge. Moreover, frequent intravitreal injections are not desirable due to the risk of surgery. Although some treatments to slow the progression of AMD are available, there is currently no cure for this irreversible disease. For Wet AMD, intravitreal injection of therapeutic agents (commercially available as *Eylea*®, *Lucentis*®, or *Avastin*®) that block vascular endothelial growth factor (VEGF) helps the patient to mitigate the symptoms only for 4–8 weeks; therefore, repeated therapy of these intraocular injections at monthly intervals in patients with wet AMD is required to preserve their vision. Nanotechnology can devise novel

Table 11.4 Top-listed US FDA approved products for AMD during the last decade in chronological order

Ocular condition	Formulation	Trade name/company	Active agent/ mechanism of action	Therapeutic indication	Approved year
Age-related macular degeneration (AMD)	Intravitreal injection	Eylea (Regeneron Pharmaceuticals)	Aflibercept (VEGF inhibitor)	Neovascular type AMD	November 2011
		Lucentis (Genentech)	Ranibizumab	Neovascular (wet) age-related macular degeneration	June 2006
		Macugen (Eyeteck Pharmaceuticals)	Pegaptanib (Pfizer)	Wet age- related macular degeneration	December 2004
	Injection or photosensitive therapy/laser (non-thermal) therapy using red light	Visudyne (QLT Phototherapeutics)	Verteporfin	Wet AMD	April 2000
	Injection or photosensitive therapy/laser (non-thermal) therapy using red light	Visudyne (QLT Phototherapeutics)	Verteporfin	Wet AMD	April 2000

approaches to target VEGF and simultaneously can assist in reducing the injection frequency.

Other therapies such as argon laser for the photocoagulation of abnormal vessels, photodynamic therapy with verteporfin, and vitreoretinal surgery are also being employed (Lin et al. 2015). Table 11.4 summarizes the top-listed range of ophthalmic products or devices approved by US FDA for the AMD condition during the last decade.

11.4.4.3 Pathobiogenesis and Mechanism

This multifactorial disease occurs due to environmental as well as genetic factors. It involves damage to the macula (a part of retina) which causes irreversible loss of central field of vision [i.e., sharp/fine details cannot be seen at far and near distance (e.g., inability to read, drive, see color, and recognize face), or “straight head vision loss”]. The exact causes and underlying pathophysiological mechanisms for AMD are yet to be fully understood. Among several forms of AMD, it can be classified primarily into two types: dry AMD (involve 90% of cases and

undergoes slow progression) and wet AMD (rarely involves only 10% of the cases and results in severe progression). It has been investigated that wet AMD affects one eye at a time, and it takes nearly more than 5 years of period to develop this condition in another eye in the majority of the wet AMD population (Birch and Liang 2007). The cascade of events and detailed mechanisms of progression of the disease have been elucidated in Fig. 11.8.

Several preclinical investigations have established the efficacy of nutraceuticals and functional foods rich in antioxidants in conjunction with anti-AMD pharmacological treatments. However, a new dimension of the role of gut microbiome in the pathophysiology of AMD has been the focus of scientific attention in recent years (Andriessen et al. 2016). The alteration of gut microbiota has been associated with various intestinal and extraintestinal disorders or inflammatory conditions (inflammatory bowel disease, colon cancer, obesity, and fatty liver disease) causing permeation of endotoxin lipopolysaccharides and pathogen-associated molecular pattern molecules, which ultimately induce low-grade

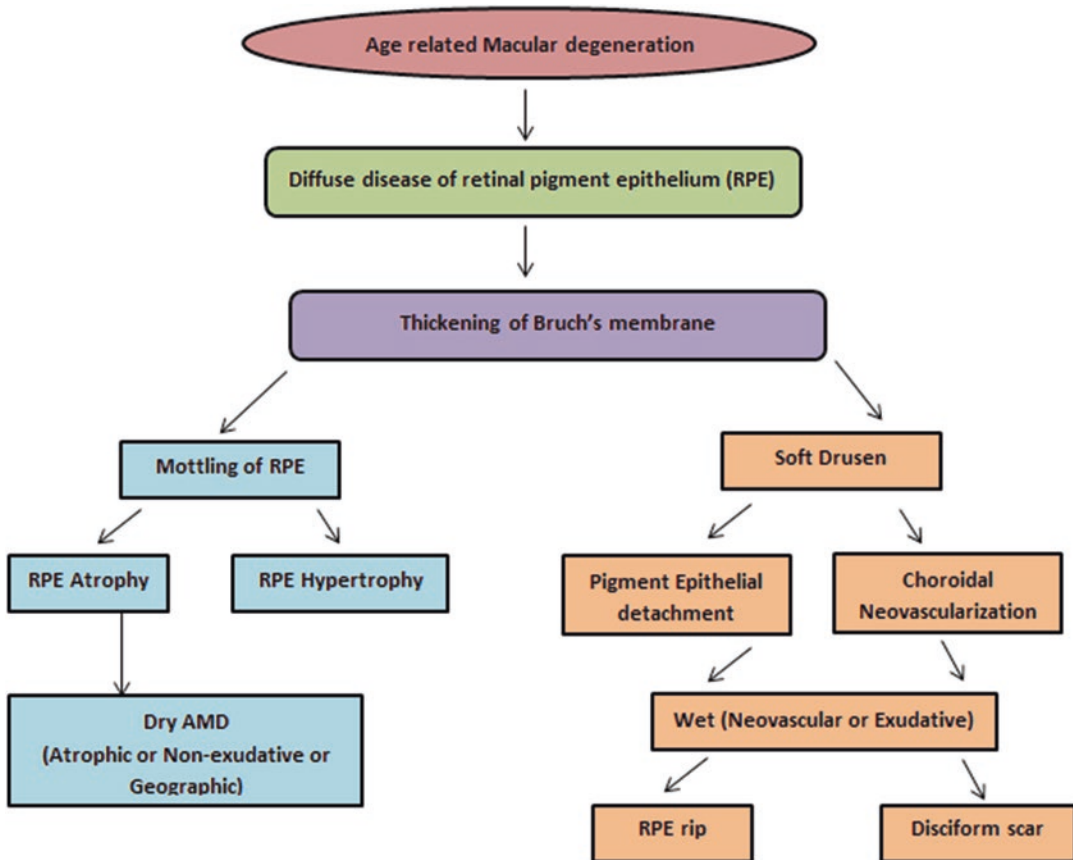


Fig. 11.8 Pathophysiology of various types of AMD

inflammation through pattern recognition receptors. Scientific reports have revealed similar links or concepts of “gut–retina axis” in the pathogenesis of ocular conditions (such as in case of RPE cells in AMD) (Rinninella et al. 2018). Further, some studies have underscored the significant immunomodulatory role of ocular and non-ocular microbiota (low diversity microbiome) and their compositional changes in various ocular and retinal disorders including AMD (Ozkan and Willcox 2019).

11.4.4.4 Dry AMD

The dry AMD (also known as atrophic or non-exudative AMD or geographic atrophy) occurs due to thinning of the macula with an accumulation of yellowish deposit, a protein ‘lipofuscin’ as tiny clumps within the retinal pigment epithelial (RPE) cells known as ‘drusen grow’ which is

a non-curable condition. The accumulation of these clumps leads to the gradual death of associated photoreceptors, and then, the patients progressively become blind. It has been found that the disease progression of dry AMD is quite slow with respect to wet AMD. Dry AMD is often difficult to diagnose in early stages. The stages of AMD are characterized by early, intermediate, and late.

The soft *drusen* of particle size $<63\ \mu\text{m}$ indicate early-stage characteristics and dry nature of AMD, which are the discreet, round, and slightly elevated clumps capable of causing hyperpigmentation or hypopigmentation within the RPE of the macula and fundus in the eyes. A small number of medium drusen ($63\text{--}125\ \mu\text{m}$ in size) also lie under the retina. However, the intermediate form of AMD is characterized by at least one large druse ($>125\ \mu\text{m}$). Late form of AMD is

quite threatening leading to irreversible vision loss. The overlying RPE indicates thinning, whereas RPE between *drusen* is indicative of thickening (De Jong 2018).

11.4.4.5 Wet AMD

The wet AMD (as known as neovascular or exudative AMD) is the leading cause of central vision loss due to macular edema from vascular hyperpermeability (i.e., leakage of blood and fluid under the macula) and abnormal new blood vessel growth behind the macula (Daruich et al. 2018).

Basically, the movement of the growth of new blood vessels occurs from the side of the retina and tends to grow toward the center. The newly formed blood vessels (which happen to be very fragile and tend to leak easily) initiate from the choriocapillaris (through Bruch's membrane) under or above the retinal pigment epithelium (RPE). Finally, the growth of blood vessels moves toward macula within a span of a few weeks. The abnormal blood vessel growth tends to reoccur even till years. The consequence of this growth is hemorrhage, scar formation, retinal detachment, and irreversible loss of central field of vision with 2 years from the day of its progression in most of the cases (if left untreated).

The pathophysiological mechanism of AMD involves multifactorial pathogenesis. IL-17 pathway has been reported to be involved in the AMD pathogenesis (Parmeggiani et al. 2012; Kauppinen et al. 2016). Further, studies have shown that vascular endothelial growth factor (VEGF), a protein essential in angiogenesis and vascular hyperpermeability, is highly associated with wet AMD (Pechan et al. 2014; Al-Khersan et al. 2019). Some studies have reported the identification of few genetic factors (such as the complement factor H (CFH) Y402H polymorphism) responsible for AMD (Landowski et al. 2019).

Another significant factor that plays a critical role in vascular leakage and neovascularization is the angiopoietin pathway (Ng et al. 2017; Saharinen et al. 2017). Angiopoietin-2 inhibitors such as RG7716 and nesvacumab are under the developmental phase and have been investigated for their potential role (in the angiopoietin path-

way) by Genentech and Regeneron Pharmaceuticals, respectively (Hussain and Ciulla 2017). Further, AKB-9778 another molecule under investigation (Aerpio Therapeutics) activates Tie-2 an intermediate found in endothelial cells that plays a key role in the angiopoietin pathway.

Integrins are transmembrane proteins that are involved in regulating cellular adhesion, kinase signaling pathways, endothelial cell migration, apoptosis, VEGF receptor-2 activation, and vascular development, making them potential targets for wet AMD therapy. Two integrin inhibitors, *Volociximab* (Ophthotech) and *Luminate* (Allegro Ophthalmics), have demonstrated good safety in phase I trials.

Moreover, several attempts have been made to identify biomarkers; for instance, carboxyethylpyrrole and C-reactive protein have been found to be associated with the pathogenesis of AMD. Investigators while studying the proteomic characterization of drusen observed that carboxyethylpyrrole adducts were abnormally high in AMD than in normal Bruch's membrane/RPE/choroid tissues. The formation of CEP protein adducts results from docosahexaenoate containing lipids (found in abundance in ocular tissues) which are responsible for free radical-induced oxidative stress in AMD (Crabb et al. 2002). Further, elevated plasma levels of carboxyethylpyrrole adduct and C-reactive protein have been reported in AMD donors as well (Renganathan et al. 2013; Chirco and Potempa 2018).

Diagnostic Tests These techniques are employed to screen and diagnose the condition at various stages, which include the Amsler test, preferential hyperacuity perimetry, shape discrimination hyperacuity, macular mapping test, and noise-field (entoptic) perimetry (Singh et al. 2017).

11.4.4.6 Conversion from Dry to Wet AMD

The ground reality is all patients initiate with the dry form of AMD in their earlier form of disease. At present, there is no diagnostic technique or method available to predict the time and state of the disease when the dry form will get converted

to wet AMD. This is primarily due to the uneven pattern of AMD, as sometimes dry AMD results in blindness without undergoing conversion into wet form. As the dry AMD undergoes slow progression, it is highly difficult for the patient and the physician to detect the initiation point and endpoint of the disease. Further, some patients suddenly turn into wet AMD and within a span of years undergo choroidal neovascularization. Therefore, the exact etiology and mechanism of conversion of dry state to wet state of AMD are fully understood; however, investigations have clearly shown that change in the pigmentation within the RPE is the prime causative or risk factor for the conversion of dry AMD into Wet AMD.

11.4.4.7 Role of Nanotechnology in AMD

With the inception of anti-VEGF aptamers in 2004 (Macugen, Pegaptanib Sodium; OSI Pharmaceuticals, NY, USA) and monoclonal antibody in 2006 (Lucentis; Ranibizumab; Genentech, California, USA), the growth of biopharmaceutical drug (protein/peptide-based therapies) market has presented spectacular evolution. It is estimated that global sales of biopharmaceutical drugs for ophthalmic indications may touch \$35.7 billion by 2025.

Nanotechnology can provide a possible solution to manage the AMD by prolonged drug delivery, administration of nanoparticle-based enzyme formulation to dissolve and metabolize lipofuscin intracellularly. The nanotechnology-based targeted delivery of anti-VEGF therapies would suppress the growth factor and will assist in the recurrence of choroid neovascularization (Hussain and Ciulla 2017). Table 11.5 represents the various nanotechnological platforms for the management of AMD along with its associated conditions.

11.5 Formulation Issues and Challenges with Anti-VEGF Therapies

The major challenges associated with the intravitreal anti-VEGF therapies are the adverse effects that include infectious and non-infectious

endophthalmitis, retinal detachment, and enhanced IOP.

Apart from various significant caveats associated with the intravitreal administration, sterile compounding of intravitreal injections often leads to contamination (as no prefilled syringe packing is available except ranibizumab) and, thus, results in bacterial and fungal endophthalmitis. In addition, variable concentrations of active drug and silicone oil droplets have been reported with repackaged syringes of bevacizumab from the compounding pharmacies. Further, the syringes which are often utilized to administer anti-VEGF agents are not suitably designed for intravitreal administration. Therefore, these syringes tend to release silicone droplets causing “floaters” which ultimately obstruct the patient’s vision. Hence, the issues related to sterility, therapeutic efficacy, and validated packaging of the containers are still required to be addressed for better patient compliance.

11.6 Novel Agents and Therapies

Among the novel targets, VEGF is one of the most significant cellular factors determining the growth and proliferation of blood vessels. It has become the major target for wet AMD therapies such as *ranibizumab* (Lucentis®), *bevacizumab* (Avastin®), both of which target VEGF-A; *pegaptanib* (Macugen®), a selective inhibitor of VEGF165; and *aflibercept* (Eylea®), which inhibits VEGF-A, as well as placental growth factor (PGF), has become established treatments for wet AMD. *Brolucizumab*, another anti-VEGF molecule likely to get approved by FDA (Biological Licensing Application accepted in 2019), is in phase III clinical trials and can last as long as 12 weeks between treatments. *Abicipar* is another drug that is injected into the eye to target VEGF. A phase II trial shows that it can last as long as 12 weeks. Therefore, longer acting drugs can be another possibility to enhance patient compliance in wet AMD treatment. Another molecule, OPT-302, targets VEGF forms C and D, which is under phase II trials and injected in combination with a traditional VEGF inhibitor. US FDA has also approved various treatments

Table 11.5 Schematic representation of significant nanotechnological platforms used in the management of AMD and associated pathologies

Platform	Payload	Biomaterial	Function/use/target	Stage	Ref.
Carbon- dots	Hybrid aptamer nanocomposite	Bevacizumab	Hybrids showed no toxicity for both in vitro and in vivo murine animal model, and effectively inhibited VEGF-stimulated angiogenesis in choroidal blood vessels	Preclinical	Shoval et al. (2019)
Nanoparticle	Cerium oxide	Oligochitosan and alginate	The hydrogels showed control release for 2 months and suppressed inflammation and response in ARPE-19 cell lines (AMD cellular models)	Preclinical	Wang et al. (2018)
	IgG-Fab antibody	Composite pentablock copolymer (PB-1; PCL-PLA-PEG-PLA-PCL)	Sustained-release nanoformulation was demonstrated as ocular platform with in vitro cell viability in mouse macrophage cell lines	Preclinical	Agrahari et al. (2016)
	Nintedanib	UV-sensitive polymer	Intravitreal administration of UV light-triggered NP release attenuated laser-induced choroidal neovascularization (CNV) in rats	Preclinical	Huu et al. (2015)
	Triamcinolone	Folate-functionalized poly(ethylene glycol)- β -polycaprolactone (PEG- β -PCL)	RPE targeting and Neovascular AMD	Preclinical	Suen and Chau (2013)
	Integrin-binding liner RGD peptide	PLGA	Restored vision function in primate and murine macular degeneration model	Preclinical	Luo et al. 2013
	Bevacizumab	PLGA/PLA	Intravitreal administration showed in a rat model of wet AMD	Preclinical	Li et al. (2012)
	anti- α v β 3 monoclonal antibody, DM101	Gold-perfluorodichlorooctane	Restored visual function in corneal neovascularization	Preclinical	Anderson et al. (2000)

(continued)

Table 11.5 (continued)

Platform	Payload	Biomaterial	Function/use/target	Stage	Ref.
Nanowater	Axitinib	Four different polymers such as PVA, PVP, HPMC, and CMC were used	Drug loaded nanowaters successfully treated corneal neovascularization in (CNV) in a murine ocular burn model compare commercial eye drop even at a low dose range	Preclinical	Yuan et al. (2015)
Dendrimer	Gene	Hydroxyl-terminated polyamidoamine (PAMAM)	Dendrimer-gene complex showed effective gene transfection in RPE cells	Preclinical	Mastorakos et al. 2015
Liposome	Small interfering RNA (siRNA)	Arg(R)-Gly(G)-Asp(D) motif peptide conjugated to PEGylated liposomes	The peptide modified liposomes targeted RPE cells and enhanced the delivery of siRNA fourfold more than non-modified liposomes	Preclinical	Chen et al., (2011, 2013)
Verisome	Visudyne®; Verteporfin	Lactose monohydrate, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate, and butylated hydroxytoluene (E321)	Photodynamic therapy with light-activated drug Verteporfin (commercialized by QLT phototherapeutics; 2002)	Phase III	NCT00121407
Hydrogel	Biodegradable polymeric system	Triamcinolone acetonide	Verisome™ is an injectable, biodegradable, and effective delivery system for sustained intraocular administration	Phase I/II	NCT01175395
Micelle	Polycaprolactone dimethacrylate (PCM) and hydroxyethyl methacrylate (HEMA)	Bevacizumab	The delivery platform successfully exhibited sustained release of bevacizumab in suprachoroidal space of SD rats for 4 months	Preclinical	Tyagi et al. (2013)
Micelle	Chitosan nanoparticle coated with cationic lipid	Triamcinolone acetonide	The micellar gel system showed sustained release for one year after intravitreal injection	Preclinical	Jiang et al. (2012)
Micelle	Polyion complex (PIC) micelle	Plasmid DNA	IV injection of polyion complex (PIC) micelle encapsulating plasmid DNA (pDNA) showed significant inhibition in CNV in a mice CNV model	Preclinical	Iriyama et al. (2011)

and therapies for neovascular age-related macular degeneration (AMD) and complications associated with diabetic retinopathy requiring frequent anti-VEGF intravitreal injections.

Anti-VEGF therapies are injected into the vitreous, where they bind to abnormal VEGF proteins and prevent them from stimulating further blood vessel growth and leakage. Therefore, frequent intravitreal injections require technicians to handle the patient and precision-based delivery. However, it becomes burdensome for the patient as well as for the practitioners to provide injection therapy at regular intervals and sometimes involves the risk for surgery.

Nanotechnology has contributed immensely to innovating noninvasive therapeutic platforms or minimally invasive technologies that are under various phases (phase I/II or III) of clinical investigation for the safe and effective administration of anti-VEGF therapies in AMD as displayed in Table 11.6. Most recently, a surgically refillable port delivery system (PDS) which can be refilled (once the delivery system runs out of the drug completely) in the wall of the eye for slow release of drug *Lucentis*® is in phase II trials and is expected to complete in 2019. This novel approach may provide a big relief to wet AMD patients requiring frequent intraocular injections. Sunitinib, another anti-VEGF receptor agent, is in phase II trials and has shown good potential as a sustained-release depot (known as version GB-102) by injecting into the eye as well as for oral administration (known as version X-82). Moreover, some physicians have reported patients becoming nonresponsive or less effective to repeated anti-VEGF injection therapies at some point in time during the therapy. Hence, this prompted the ophthalmic clinicians to look for new targets in wet AMD.

11.6.1 Stem Cell Therapies

Various reports have shown the induction of pluripotent stem cells (iPSCs) which differentiate into photoreceptors and RPE cells and integrate into the host cell structure to significantly improve the retinal function in retinal dystrophic

and degenerative rat and mouse models (Kanemura et al. 2014). Further, stem cells are also being injected into the eye in trials for dry AMD. Some studies have revealed that if stem cells are injected precisely within the clinical trials, they can be therapeutically helpful; however, treatments outside clinics with imprecise localization and insertion may result in loss of vision. Some initial studies revealed improvement in the visual activity of patients (in the order of 9–19 letters on visual acuity test) within few months of the subretinal ESC transplantation in the Asian population affected with wet AMD. The study showed the huge potential of stem cells as a regenerative therapy in AMD (Song et al. 2015). Furthermore, in another investigation, subretinal transplantation of iPSC-derived RPE cells was premeditated in advanced wet AMD patients. Although no improvement in the visual acuity was observed, however, no worsening of the condition post one year of transplantation was reported (Mandai et al. 2017). The study yielded no significant outcome in terms of therapeutic efficacy, but still it is a big matter of investigation and debate that why the diseased condition was not progressed. Thus, in the light of above facts, it can be implied that the role of stem cell therapy is still in its nascent stages and more investigations are required to implement this therapy at a specific endpoint of the disease for better results.

11.6.2 Gene Therapies

More attention has been paid to the potential of gene therapy in AMD, the delivery of nucleic acid polymers into host cells to treat retinal diseases in recent times. The gene therapy could be exploited to ameliorate the burden of chronic intravitreal therapy via the expression of anti-VEGF proteins. Phase I investigations have shown the application of adeno-associated virus vector (such as AAV2 and AAV8 encoding genes for anti-angiogenic proteins) delivered RPE derived factor gene in advanced stages of neovascular AMD (Moore et al. 2017). Further, endogenous expression of various VEGF inhibitors (such as soluble fms-like tyrosine kinase-1 and

Table 11.6 List of few ophthalmic devices/delivery systems under clinical investigation for the management of AMD

Drug/dosage form	Therapeutic indication	Stage	Manufacturer/stage of development	Manufacturer/stage of development	Reference/trial no.
Intravitreal implant	Dry AMD	Phase II	Allergan Inc.	Polymeric device/excipient Intravitreal implant containing brominidine tartrate	NCT02087085
IVT (Verisome®) of triamcinolone acetonide	AMD	Phase I/II	Verisome™ is an injectable, biodegradable gel for sustained intraocular administration	Biodegradable gel	NCT01175395
Liposomal formulation PDT with light-activated Verteporfin (Visudyne®)	Wet AMD	Phase III	QLT phototherapeutics	Systemic route; composed of lactose monohydrate, egg phosphatidylglycerol, dimyristoyl Phosphatidylcholine, ascorbyl palmitate, and BHT	Visudyne® product information EMA (http://www.ema.europa.eu); NCT00121407
Semipermeable hollow fiber membrane NT-501 implant	AMD	Phase I/II	Renexus & Noah Group	Semipermeable hollow fiber membrane with ciliary neurotrophic factor producing RPE cells	NCT00447954
NT-503 implant	AMD	Phase I/II	Neurotech	Semipermeable hollow fiber membrane with VEGF receptor Fc-fusion protein (VEGFR-Fc)-releasing cells	NCT02228304
Photrex® (liposomal Rostaporfin)	AMD	Phase III	Mitravant Medical Technologies	Liposomal formulation of Rostaporfin for intravitreal injection	NCT00157976
PDDS® Ranibizumab	AMD	Phase II	Genetech, ForSight vision 4 Inc.	Novel refillable system designed to provide release rate of 10 mg/ml for decreasing macular thickness and choroidal neovascular leakage	NCT02510794

iTrack microcatheter (a triamcinolone acetate-based DDS)	Neovascular AMD	Phase I, II	iScience Interventional; Janssen Research & Development	Injection device for suprachoroidal delivery of TA	NCT01226628
LADDER (long-acting delivery of ranibizumab)	Wet AMD	Phase II	PDS, Genentech	Sustained-release port delivery system for ranibizumab	Campochiaro et al. (2019); and NCT02510794
SalutarisMD treatment	Wet AMD	Phase I	Salutaris Medical Devices, Inc. USA	Using radiation (strontium 90 radioisotope) to cause the AMD lesions to regress	NCT02988895
The IRay™	Wet AMD	Phase II	Oraya therapeutics, USA	Three tightly focused, low-energy beams of X-ray radiation using special contact lens	NCT01016873
The AdaptDx dark adaptometer	Wet AMD	Phase I	Maculogix Inc. PA, USA	A tabletop device (FDA approved, 2008) tests the patients into darkened tunnel and focuses on a red dot, which lights the center of a viewing screen	NCT03225131

sFLT-1) has also been explored for binding and neutralizing VEGF-A. It is a well-documented fact that the success of gene therapy for management of AMD depends on various factors such as selection of therapeutic protein, expression level, associated adverse effects, optimized vector, promoter, and method of transfection.

RGX-314 is an anti-VEGF treatment delivered by AAV-associated gene therapy that has been approved by the FDA for another disease known as *Leber's congenital amaurosis*. This could pave the way to the potential application of gene therapies in diverse retinal conditions of AMD.

11.6.3 Complement-Associated Specific Targeted Therapies

The complement system, an intrinsic component of innate immunity, imparts a significant role in maintaining immune surveillance and homeostasis of ocular microenvironment (Park et al. 2019). The mechanism of complement disease dissemination is yet to be fully understood. However, the targeted modulation of complement specific proteins has emerged as a viable therapeutic approach to mitigate disease progression in AMD. Studies have shown the potential application of complement cascade inhibitors to target the modulation of complement proteins C3, C5, factor B, factor D, and properdin in AMD as listed in Table 11.7.

A phase II trial for new molecule APL-2 in combination with anti-VEGF agent is under investigation for the inhibition of complement factor C3. Avacincaptad pegol (Zimura®) is another drug targeting a different complement protein, C5. The literature studies have revealed dysregulation of gene encoding complement factor H, and patients having a copy of Y402H polymorphism (a tyrosine-to-histidine substitution at amino acid position 402 within the CFH protein) are more susceptible to AMD (approximately fivefold increase in risk). Other factors are B, D, C2, and C3, and I have also been observed to be associated with the risk of AMD. Various other clinical studies of Potentia (C3 inhibitor), ARC1905 (C5 inhibitor), eculizumab (humanized monoclonal antibodies binding C5), Tanox (complement factor D inhibitor), and TA106 (complement factor B inhibitor) are also under investigation to assess the role of complement system in AMD.

11.6.4 Targeting Factors/Pathways—IL-7, Rap1 GTPase

The inflammatory response in macula along with various inflammatory biomarkers such as IL-7, cytokines has been found to be associated with AMD. The members of interleukin family which primarily play a vital role in the pathogenesis of AMD are IL-17A cytokine and IL-17 receptor (R)-C. Therefore, the targeting of IL-17, IL-17R-C, or cells producing IL-17 may mini-

Table 11.7 Some significant clinical trials for various complement-based therapeutics in AMD (credit: <https://clinicaltrials.gov>)

Agent/therapy	Target	Class	Clinical indication	Phase (P)/trial no.
CLG561 (Novartis)	Properdin	Antibody	AMD	P2 (NCT02515942)
APL-2 (Apellis)	C3	Peptide (PEGylated)	Geographical atrophy	P2 (NCT02503332)
LFG316 (Novartis)	C5	Antibody	AMD	P2 (NCT02763644)
Zimura (Ophthotech)	C5	Aptamer	AMD	P2/3 (NCT02686658)
Lampalizumab (Genentech)	Factor D	Antibody	AMD	P3 (NCT02247531)
IONIS-FB-Lrx	Factor B	Antibody	AMD	P2 (NCT03446144)
AMY-101	C3	Peptide	Complement-mediated diseases	P1 (NCT03316521)

mize the retinal degeneration and could be considered as a potential therapeutic target for AMD.

Rap1 GTPase (small guanosine triphosphatase, GTPase) is involved in regulating both endothelial and epithelial cell junctions (critical factor involving RPE barrier function leading to the development of AMD) (Wittchen et al. 2013). Recently in 2018, Li et al. investigated the functional role and mechanism of Rap 1 in CNV in vivo (laser-induced CNV rat model) (Li et al. 2018). It was observed from the findings that activation of Rap1 using 8CPT-2'-O-Me-cAMP was able to produce a significant reduction in CNV size and VEGF expression.

11.6.5 Miscellaneous Therapies

Several agents such as *Oracea*® (an antibiotic famously known as doxycycline) are under phase II/III investigation for the possible anti-inflammatory effects, which could be beneficial in patients with geographic atrophy (or dry AMD). Antidiabetic drugs like metformin have also been explored for an anti-inflammatory role in AMD. Agents such as lipoic acid are being tested in dry AMD patients for their antioxidant properties. This agent has shown immense application by protecting the retinal degeneration in preclinical models of mice.

11.7 Conclusions and Current Perspectives

The confined position of the eye and the challenging eye conditions make it an excellent target for the development and testing of minimally invasive, safe, and effective nanomedical technologies. Further, the global market has also shown tremendous expansion over the last decade as eye diseases like macular degeneration, glaucoma, and diabetic retinopathy had hugely impacted the health care costs. Recent trends in ocular drug delivery care have demonstrated novel technological platforms based on nanoscale systems that can be rapidly and successfully translated into clini-

cally relevant treatments in the eye. Implantable devices such as nano-ocular pumps are capable of dispensing nanoliter-sized dose delivery for the management of glaucoma and AMD.

Nanotechnological tools have produced tangible solutions by facilitating innovative approaches generated by the clinical knowledge based on pathophysiological mechanisms. For example, nanodevices and nanosystems are capable of determining the physiology of the ocular tissues and cells (IOP or oxygen tension), valves for glaucoma drainage, prosthetics for ion channels (which are sensitive to light and can cure blindness), and tools for surgical intervention based on nanoneedles and nanotweezers.

Further, design of contact lenses with novel applications, integration of gels into drug delivery devices like intraocular pumps, injections, and implants have been devised to reduce the burden of comorbidities caused by emerging ocular conditions such as glaucoma, diabetic retinopathies, and AMD. The current summarization of literature is an attempt to provide a critical appraisal of the clinical aspects with pathophysiological bases while employing nanotechniques and novel drug delivery systems used in the characterization of ophthalmic products along with a thorough insight into the safety and biocompatibility of these systems. Finally, a new dimension has been added in the ocular drug delivery segment with the design of stimuli-responsive gels, molecularly imprinted gels, and 3D printed nanogels/hydrogels; 3D printed devices comprise ophthalmic gels. This novel application of gelling systems would generate huge currents in the treatment and management of ocular drug delivery markets by paving a way forward in the production of artificial corneas, corneal wound healing, and hydrogel-based contact lenses.

In the light of above-discussed summary, it can be remarked that nanotechnology-based treatments offer immense potential and application in overcoming the complications (such as diffusional limitation and ocular barriers) by improving the therapeutics in the field of ocular nanomedicine, nanodevices, and tissue regeneration. It can revolutionize the methodology of

ocular drug delivery (such as treatment-based IOP-independent therapies in glaucoma) via targeted or controlled or microelectromechanical approaches.

Conflicts of Interest There are no conflicts of interest to declare.

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