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New Drugs in the Pipeline for the Management of AMD

Ana Marta and Bernardete Pessoa

Abstract

Anti-vascular endothelial growth factor (anti-VEGF) therapies have revolutionized the care of patients with retinal diseases. In the 1990s, it was observed that anti-VEGF antibodies reduced tumor angiogenesis, and consequently, these antibodies started to be used off-label in the exudative form of age-related macular degeneration (AMD). In the 2000s, research was directed towards the development of anti-VEGF therapies for retinal disease management. Several anti-VEGF therapies were approved: pegaptanib, an RNA aptamer, in 2004; ranibizumab, an anti-VEGF F_{ab}, in 2008; aflibercept, a humanized IgG F_c, in 2011; and brolucizumab, an scFv, in 2019. Currently, new therapeutic options are emerging, and approval is expected soon. These new therapies aim to increase treatment durability and thus reduce treatment burden and improve real-world outcomes. In this chapter, the mechanisms of action and the preliminary trial results of these potential new therapies will be described.

Keywords: AMD, drug therapy, intravitreal injections, clinical trials, pipeline

1. Introduction

Global prevalence estimates suggest that approximately 196 million people lived with age-related macular degeneration (AMD) in 2020. Of these, 10.4 million people were living with moderate to severe vision impairment. In 2030, AMD is estimated to affect 243 million people due to aging [1]. The pathogenesis of AMD results from complex multifactorial interactions, including metabolic, genetic, and environmental [2]. AMD has been classified into two major subtypes: non-exudative or dry AMD and exudative or wet AMD. Although dry AMD represents 90% of patients, exudative AMD causes more severe loss of vision, being the target of most investigations [3]. These patients require very regular clinic visits, and the chronicity of anti-vascular endothelial growth factor (anti-VEGF) therapy can substantially impact the quality of life of the patient and the caregivers [4, 5]. This decrease can compromise anti-VEGF therapy compliance and explain the undertreatment of patients observed in real-world studies and the waiver of patients involved in clinical trials [6, 7]. New trials are focusing on improving the therapeutic options, particularly on the decrease of the associated burden. This chapter describes the current research on therapeutical approaches to treat the dry and exudative forms of AMD. **Figure 1** summarizes the drugs and stages of development.

The information was gathered from a medical literature review and ongoing clinical trials and their results in the area of AMD treatment using PubMed database (<https://www.ncbi.nlm.nih.gov/pubmed>). The words or medical head subjects

New drugs in the pipeline for the management of AMD					
DRY AMD	COMPLEMENT INHIBITION	NEUROPROTECTION	VISUAL CYCLE MODULATORS	CELL-BASED THERAPIES	ANTI-INFLAMMATORY AGENTS
	<p>Pegcetacoplan (Phase 3)</p> <p>Avacincaptad pegol (Phase 2/3)</p>	<p>Brimonidine tartrate (Phase 3)</p> <p>Elamipretide (Phase 2)</p>	<p>ALK-001 (Phase 3)</p>	<p>MA09-hRPE (Phase 1/2)</p> <p>CPCB-RPE1 (Phase 1/2)</p>	<p>Doxycycline (Phase 3)</p> <p>FHTR2163 (Phase 2)</p>
WET AMD	Potentially more durable anti-VEGFs	ONS-5010 AND BIOSIMILARS	TOPICAL ANTI-VEGF ± ANTI-PDGF	EXTENDED RELEASE OPTIONS	Gene therapy
	<p>Brolucizumab (Phase 4)</p> <p>Abicipar pegol (Phase 3)</p> <p>Conbercept (Phase 3)</p> <p>OPT-302 (Phase 3)</p> <p>Faricimab (Phase 3)</p> <p>KSI-301 (Phase 2)</p>	<p>ONS-5010 (Phase 3)</p> <p><u>For ranibizumab</u> (phase3): FYB201, SB11, Xlucane...</p> <p><u>For aflibercept</u> (phase3): ABP 938, FYB203, SB15...</p>	<p>Squalamine lactate (Phase 2)</p> <p>PAN-90806 (Phase 1/2)</p>	<p>PDS (Phase 3)</p> <p>GB-102 (Phase 2)</p> <p>NT-503 (Phase 1/2)</p> <p>Aflibercept Hydrogel Depot (preclinical)</p> <p>pSivida Durasert Technology (preclinical)</p>	<p>RGX-314 (Phase 2)</p> <p>PF-655 (Phase 2)</p> <p>ADVM-022 (Phase 1)</p> <p>Retinostat (Phase 1)</p> <p>AAV2-sFLT01 (Phase 1)</p> <p>AAVCAGsCD59 (Phase 1)</p>

Figure 1.
Summary of new drugs in the pipeline for the management of age-related macular degeneration (AMD).

used were: AMD and clinical trials. All relevant articles were imported into Zotero (Version 5.0, Center for History and New Media at Universidade George Mason, USA), and duplicate articles were deleted. We selected the promising therapies according to action mechanisms and excluded all therapies that had failed in clinical trials. Comments, editorials, and articles not written in English were not analyzed.

2. For dry AMD

2.1 Complement inhibition

Although lampalizumab (anti-factor D Fab) and eculizumab (inhibitor of the activation of terminal complement) failed to slow geographic atrophy progression, the complement system has been implicated in the pathogenesis of geographic atrophy, and so, research on how to inhibit the complement system did not stop [8, 9].

Pegcetacoplan (APL-2; Apellis Pharmaceuticals, Waltham, Massachusetts, USA) is a synthetic molecule that selectively inhibits C3, effectively downregulating all three complement pathways. Phase 2 of the FILLY clinical trial compared patients receiving intravitreal injection (monthly and bi-monthly) with a control group. The results showed a 29% reduction in the rate of geographic atrophy and a better outcome in the monthly injection group. Moreover, it was observed that the risk of neovascular AMD was higher (18%) in the group subjected to monthly injections when comparing with the group subjected to bi-monthly injections (8%) and with the control group (1%) [10]. A phase 3 trial is currently in the recruitment phase (NCT03525600) [11].

Avacincaptad pegol (Zimura; Iveric Bio, New York, New York, USA) is a C5 inhibitor. Phase 2/3 GATHER1 clinical trial showed a significant reduction of geographic atrophy growth over 12 months, probably due to C3 activity preservation. A second confirmatory trial (GATHER2) is underway [12].

2.2 Neuroprotection

Retinal neuroprotection strategies have been studied for dry AMD, including apoptosis and necrosis prevention, and oxidative injury reduction [13].

Elamipretide (Stealth Biotherapeutics) is a mitochondria-targeted drug thought to reduce mitochondrial dysfunction. Phase 1 of the ReCLAIM clinical trial showed that elamipretide was safe, well-tolerated and that this drug may improve vision in patients with intermediate AMD, manifested as high-risk drusen [14]. Phase 2 ReCLAIM-2 clinical trial is underway [15].

Brimonidine tartrate (Allergan) is best known in glaucoma as the intraocular pressure (IOP) lowering agent. Phase 2A of the BEACON clinical trial assessed the intravitreally delivery of brimonidine through a delayed delivery system. Results showed a lower rate of geographic atrophy progression, although not statistically significant [16]. Phase 2B of the BEACON clinical trial demonstrated a reduction in geographic atrophy progression using higher doses of brimonidine [17]. Phase 3 of IMAGINE and ENVISION clinical trials are being designed [16].

2.3 Visual cycle modulators

One of the earliest changes in the retina that precede AMD symptoms is the formation of toxic vitamin A dimers.

ALK-001 (Alkeus Pharmaceuticals) is a chemically modified form of vitamin A that replaces the vitamin A in the body to prevent toxic vitamin A dimers. Studies demonstrated functional preservation of visual function in animal models [18]. Phase 3 of the SAGA clinical trial will measure the extent to which treatment with the oral capsule of ALK-001 slows geographic atrophy progression [19].

2.4 Cell-based therapies

Cell therapy is an alternative strategy when the naturally existing cells are already too damaged to be preserved using neuroprotective agents. Human pluripotent stem cells (hPSCs) comprise human embryonic stem cells (hESCs) and human-induced pluripotent stem cells (hiPSCs). There are two subtypes of cell-based treatments: stem cell therapies that involve delivering new retinal pigment epithelial (RPE) cells to the subretinal space, and non-stem cell therapies based on cell implantation, which generates protective factors [20].

MA09-hRPE (Astellas Pharma) is hESC-derived Retinal Pigment Epithelium (hESC-RPE). The phases 1/2 clinical trial results confirmed that hESC-derived cells could serve as a potentially safe new source for regenerative medicine [21–23].

CPCB-RPE1 (The California Project to Cure Blindness-Retinal Pigment Epithelium1) is a polarized monolayer of hESC-RPE ultrathin, synthetic parylene substrate designed to mimic Bruch's membrane. This therapy involves a subretinal implant. It was demonstrated the feasibility and safety of CPCB-RPE1 subretinal implantation in a comparable animal model [24]. Phase 1/2A of the clinical trial suggests that CPCB-RPE1 may improve visual function [25, 26].

2.5 Anti-inflammatory agents

Inflammation has been implicated in AMD pathogenesis and progression, even though it is no classical inflammatory disease like uveitis [27].

Doxycycline (Oracea; Galderma Laboratories, Fort Worth, Texas, USA) is an antibiotic that belongs to the tetracycline class of antibiotics and plays a role in immunomodulation, cell proliferation, angiogenesis, and the regulation of inflammation. Phase 3 of the TOGA clinical trial includes patients with geographic atrophy randomized in groups treated with Oracea® or placebo. The results are pending [28].

FHTR2163 (Genentech/Roche) is a new antibody delivered by intravitreal injection that inhibits the HTRA1 gene associated with geographic atrophy. Phase 2 of the GALLEGRO clinical trial will evaluate the safety, tolerability, and efficacy of intravitreal injections of RG6147, administered every four or every eight weeks for a total of approximately 76 weeks, in participants with geographic atrophy secondary to AMD (when compared with the sham control) [29].

3. For wet AMD

3.1 Potentially more durable anti-VEGF agents

Potentially more durable anti-VEGF agents may reduce the burden of intravitreal injections, help stabilize the disease and improve compliance with treatment.

Brolucizumab (Beovu; Novartis, Basel, Switzerland) is the most recent intravitreal anti-VEGF agent to receive FDA approval. It is a humanized single-chain antibody fragment with a molecular weight of 26 kDa. Phase 3 of the HAWK and HARRIER clinical trials showed that brolucizumab was non-inferior to aflibercept regarding visual function as at week 48, more than 50% of the eyes treated with 6 mg of brolucizumab were maintained on q12w dosing intervals. Moreover, anatomic outcomes favored brolucizumab over aflibercept, and the overall safety results were similar between the two drugs [30].

Abicipar pegol (Allergan) is a novel class of molecules referred to as designed ankyrin repeat proteins (DARPin) that bind VEGF-A. DARPins are smaller and have a high affinity to VEGF, leading to greater stability and a longer-acting effect. The results of phase 3 of the SEQUOIA and CEDAR clinical trials showed that the eight and 12-week abicipar regimens were non-inferior to the ranibizumab's monthly regimen, but patients had a much higher risk of developing intraocular inflammation (15% and 15.4% vs. 0%) [31–33]. The company modified the manufacturing process after finding impurities in the formulation, and subsequently, the MAPLE study showed a decrease in the incidence of intraocular inflammation to 8.9% [34]. A license for abicipar pegol was already submitted to the *Food and Drug Administration* and the European Medicines Agency.

Conbercept (Chengdu Kanghong Biotech Co., Ltd.) is an antibody that targets VEGF-A, VEGFB, VEGF-C, and placental growth factors. It was approved to treat exudative AMD in China in 2013. Phase 2 of the AURORA and phase 3 of the PHOENIX clinical trials showed the safety and efficacy of conbercept with three initial monthly treatments followed by quarterly treatments compared with the sham group [35, 36]. Phase 3 of the PANDA-1 and PANDA-2 global clinical trials compare maintenance doses of conbercept every 8 or 12 weeks with doses of aflibercept every eight weeks; results are expected in 2022 [37, 38].

OPT-302 (Opthea Limited) is a soluble form of the human VEGF receptor-3 (VEGFR-3), expressed as an Fc-fusion protein molecule designed to inhibit VEGF-C and VEGF-D. Results from phases 1 and 2 of the ShORe and COAST clinical trials showed that this molecule was safer and had better visual outcomes than ranibizumab alone [39, 40]. Phase 3 of the ShORe and COAST clinical trials will be double-masked and sham-controlled. Treatment-naïve patients will be enrolled to assess the efficacy and safety of 2.0 mg OPT-302 combined with anti-VEGF-A therapy by comparison with anti-VEGF-A monotherapy (standard of care). Opthea expects to initiate patient recruitment in the first half of 2021 [41].

Faricimab (Roche, Genentech) is a novel bispecific antibody that targets both angiopoietin-2 (Ang-2) and VEGF-A. Phase 2 of the STAIRWAY clinical trial

suggests that faricimab can be an effective maintenance therapy for exudative AMD with a dosing interval of 16 weeks [42, 43]. Phase 3 of the TANAYA and LUCERNE clinical trials will compare faricimab given every 16 weeks with aflibercept given every eight weeks [44, 45]. FDA requests for faricimab are expected to occur in 2021 for diabetic macular edema and in 2022 for exudative AMD.

KSI-301 (Kodiak Sciences) is a novel intravitreal, anti-VEGF antibody biopolymer conjugate designed to block all VEGF-A isoforms. Phase 1 of the DAZZLE clinical trial showed excellent safety, strong efficacy, and considerable durability in most patients for three or more months [46]. Phase 2 of the DAZZLE clinical trial is a prospective, randomized controlled clinical trial designed to evaluate the safety and efficacy of KSI-301 [47].

3.2 ONS-5010 and biosimilars

ONS-5010 (Outlook Therapeutics, Inc) is an ophthalmic formulation of bevacizumab. Phase 3 clinical trials compare monthly doses of ONS-5010 with a ranibizumab regimen of 3 monthly doses followed by quarterly doses [48]. FDA approval is expected in 2021 or 2022, and 12 years of exclusivity, protecting against bevacizumab biosimilars, are expected.

FYB201 (Formycon and Bioeq), SB11 (Samsung Bioepis), and Xlucane (Xbrane Biopharma) are biosimilars for ranibizumab under development that are expected to reach the market in less than one year when the patent for ranibizumab expires [49–51].

Aflibercept biosimilars are in phase 3 of clinical trials and are expected to reach the market between two and three years when the patent for aflibercept expires.

3.3 Topical anti-VEGF ± anti-PDGF

Although regorafenib, pazopanib, and LHA510 failed, other therapies showed promising results [52–54]. These formulations have the great advantage of being less invasive, but they can decrease the possibility of monitoring treatment compliance, as it happens with glaucoma patients medicated with lowering ocular hypertension drops.

PAN-90806 (PanOptica) is a topical formulation of a small molecule, a tyrosine kinase inhibitor (TKI), to treat wet AMD. In phase 1/2 of a dose-ranging clinical trial, more than half of patients receiving PAN-90806 once a day for 12 weeks completed the study without needing anti-VEGF rescue therapy. Fourteen of the 51 patients in the study, 88% experienced clinical improvement of their condition or their disease's stability [55].

Squalamine lactate (Genaera Corporation) is an amino sterol derived from the dogfish shark's cartilage that blocks VEGF, PDGF basic fibroblast growth binding calmodulin and its chaperones. A phase 2 clinical trial showed improved vision when squalamine lactate was used in combination with anti-VEGF treatments [56, 57].

3.4 Extended-release options

The extended-release options may also reduce the burden of intravitreal injections.

The port delivery system (PDS; Hoffmann-La Roche) is a permanent, refillable implant, which is surgically placed at the pars plana through an incision in the sclera. PDS continuously releases concentrated ranibizumab by passive diffusion into the vitreous cavity.

Phase 2 of the LADDER clinical trial showed similar functional and anatomical outcomes after nine months of treatment with ranibizumab delivered through PDS or monthly intravitreal injections of ranibizumab [58, 59]. The mean time for the first PDS refill was 15 months, with 80% of patients not requiring a PDS refill for six or more months. Phase 3 of the ARCHWAY clinical trial is ongoing [60].

GB-102 (Graybug Vision) is a depot formulation of sunitinib malate that might need only 2 or 3 treatments per year [61]. Phase 2 of the ALTISSIMO clinical trial evaluated the safety and effect duration of GB-102 intravitreal injections administered every six months compared to aflibercept intravitreal injections administered every two months [62]. The results are currently pending.

NT-503 (Neurotech Pharmaceuticals) is a biological sustained drug delivery device that can provide anti-VEGF therapy's continuous delivery. Preliminary studies show that the device can be implanted safely in humans [63]. The results of phases 1 and 2 of clinical trials are pending [64].

Aflibercept Hydrogel Depot (Regeneron Pharmaceuticals and Ocular Therapeutix™) is a delivery system based on a PolyActive hydrogel copolymer's microparticles. In studies with animals intravitreally injected with aflibercept hydrogel depot a, sustained and controlled release of aflibercept was achieved. No adverse effects in the eyes of healthy rhesus macaques were observed for up to 6 months [65].

pSivida Durasert Technology (EyePoint Pharmaceuticals, Inc.) can be used to deliver different drugs for extended periods (months or even years) with a single application. Delivery of a tyrosine kinase inhibitor in animals provided promising results [66].

3.5 Gene therapy

Gene therapy is based on the insertion of an anti-VEGF coding sequence into retinal cells' DNA through a viral vector.

ADVM-022 (Adverum) produces an anti-VEGF-A fusion protein delivered through intravitreal injection via the AAV.7 m8 viral vector. Phase 1 of the OPTIC clinical trial showed that treatment with a single injection prevented additional anti-VEGF treatment over six months [67, 68].

RGX-314 (RegenexBio) (Rockville, MA, USA) produces an anti-VEGF A fab delivered through a subretinal treatment via an AAV8 viral vector. Phases 1/2a of the AAVIATE clinical trial showed a decrease in injection burden without significant inflammation or adverse effects [69]. Phase 2b of the AAVIATE clinical trial will explore a suprachoroidal injection [70].

Retinostat (Oxford BioMedica) is a lentiviral vector expressing endostatin and angiostatin to inhibit angiogenesis potentially. Phase 1 clinical trial showed that the LentiVector® gene therapy platform safely and efficiently delivered genes to the retina resulting in stable, long-term expression [71].

AAV2-sFLT01 (Genzyme, a Sanofi Company) is a vector that expresses a modified soluble Flt1 receptor designed to neutralize the proangiogenic activities of VEGF via an intravitreal injection. Phase 1 clinical trial showed that AAV2-sFLT01 was safe and that there was good tolerance to this vector [72]. After three years of follow-up, AAV2-sFLT01 appears to be generally safe, well-tolerated and does not appear to raise any new safety concerns [73].

AAVCAGsCD59 (Hemera Biosciences) is a molecule that targets the terminal step of complement activation that leads to the formation of the membrane attack complex. Two-phase 1 clinical trials for both exudative and dry AMD showed that subretinal injection of AAV-CD59 attenuated the formation of laser-induced choroidal neovascularization by around 60% in mice, even when the site of delivery was distal to the laser-induced choroidal neovascularization site [74].

An alternative for genetic interference is small interfering RNA (siRNA) that inhibits the protein-coding genes and prevent protein synthesis. Delivery can be by the topical installation or intravitreal injection. Bevasiranib (Opko) was the first siRNA used, but it did not show efficacy in phase 3 of the COBALT clinical trial [75]. AGN211745 (Alergan) was designed to reduce pathologic angiogenesis mediated by both VEGF and bFGF. The study was terminated early due to a company decision (non-safety-related), and for this reason, certain outcome measures were not analyzed [76].

PF-655 (Pfizer) is a siRNA that inhibits expression of the hypoxia-inducible gene RTP801, which inhibits the mammalian target of the rapamycin (mTOR) signaling pathway and reduces VEGF-A production. Results from phase 2 of the MONET clinical trial showed that the combination of PF-655 with ranibizumab led to an average gain in visual acuity superior to the one observed for patients under ranibizumab monotherapy [77].

4. Conclusion

There are many potential therapeutic options for AMD. New treatment options for dry AMD that slow disease progression or re-establish retinal cells are becoming a reality. For wet AMD, new drugs that could lead to a longer half-life in the vitreous, lower costs, and more potent anti-angiogenesis activity, should be approved soon. With the increase of population longevity, AMD incidence and prevalence will most probably increase, and these therapies may reduce both the societal and individual treatment burden. Although they are in the earlier clinical trial phases, the authors consider that the cell-based therapies for dry AMD and gene therapy for wet AMD are the more promising therapies for the future because they tend to correct the source's problem. The new COVID vaccines also represent a significant step in this area, and these novel technologies may be future treatments for many other diseases.

Conflict of interest

The authors declare no conflict of interest.

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