Journal of Experimental Pharmacology

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REVIEW

Current and Future Anti-VEGF Agents for Neovascular Age-Related Macular Degeneration

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Abstract: Age-related macular degeneration (AMD) is the most common cause of legal blindness in developed countries. Neovascular (ie, wet) AMD is currently managed with intravitreal therapy. Traditional treatments (ie, bevacizumab, ranibizumab, aflibercept) provide high-efficacy therapy but can also require frequent dosing. Newer and future anti-VEGF therapies aim to decrease injection frequency through eitherlonger half life or port-delivery systems (brolucizumab, conbercept, KSI-301, ranibizumab). This review outlines current anti-VEGF treatments and ways by which their duration might be extended.

Keywords: anti-VEGF, wet age-related macular degeneration, brolucizumab, aflibercept, bevacizumab, ranibizumab, KSI-301

Introduction

Age-related macular degeneration (AMD) is the most common cause of severe vision loss in developed countries and the third–most common cause of legal blindness worldwide.[1,2] As the population ages, the magnitude of this challenge will continue to expand. AMD is forecast to affect 17.8 million people worldwide by 2050.[3,4] Moreover, the Age-Related Eye Disease Study (AREDS) reported that >25% of patients with advanced AMD in one eye will later develop advanced AMD in the other within 10 years.[5]

Central visual function, which is necessary for reading and driving, is strongly impacted by AMD. Progression in AMD may pass through multiple stages: early, intermediate, and advanced. The advanced stages of AMD take two forms: neovascular (ie, wet) AMD (wAMD), characterized by the formation of choroidal neovascularisation (CNV), and geographic atrophy in the dry form of AMD.[5] Progressive CNV activity may result in progressive fibrosis and central scarring. The formation of such scars permanently destroys photoreceptors and the retinal pigment epithelium, leading to permanent vision loss.[1]

The precise cause of wAMD is uncertain; however, upregulation of VEGF and other proangiogenic factors resulting in CNV development is an important component of neovascular disease.[6] There are five proteins that make up the VEGF family: VEGFA, VEGFB, VEGFC, VEGFD, and PGF), with different agonistic VEGF isoforms binding to different VEGF receptors.[7] VEGFA, which is simply known as VEGF due to its role as the main angiogenic factor, stimulates physiological and pathological angiogenesis and activates VEGFR1 and VEGFR2, the major receptors for angiogenesis, on endothelial cells.[7] VEGFA also has many known slice variants, including $VEGFA_{121}$, $VEGFA_{145}$, $VEGFA_{165}$, and $VEGFA_{189}$.[8]

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Received: 26 June 2021
Accepted: 6 September 2021
Published: 29 September 2021

VEGFB and PGF bind only to VEGFR1, the activation of which creates a weaker signal for angiogenesis than activation of VEGFR2.[7] VEGFC and VEGFD are tangentially involved in angiogenesis through VEGFR2, but are crucial for lymphangiogenesis via VEGFR3.[7]

Upon receipt of an angiogenic mediator (such as VEGF), pericytes detach from the vessel wall, loosening junctions between endothelial cells and increasing vessel permeability.[9,10] A new extracellular matrix is formed by the leakage of plasma proteins, leading to the growth of new blood vessels. Breaking down vascular barriers is necessary for physiologic angiogenesis; however, VEGF can also stimulate fluid exudation and leakage into retinal tissues.[6,10] VEGF also stimulates ICAM1 and VCAM1 expression in the retina and brain.[6] With enhanced response from VEGFA, inflammation and hypervascular permeability may be caused by macrophage migration.[7]

Therefore, preventing excessive angiogenic pathway activity and subsequent vascular permeability and inflammatory responses through inhibiting VEGF binding to VEGFR2 is the major focus of anti-VEGF treatments in wAMD.[11] The first anti-VEGF agent approved to treat wAMD was pegaptanib (Macugen, Bausch and Lomb), which blocks just one isoform ($VEGFA_{165}$). Later, pan-VEGF blockers, such as ranibizumab (Lucentis, Genentech/Roche) and off-label bevacizumab (Avastin, Genentech/Roche), which block all isoforms of VEGFA, supplanted pegaptanib with considerably better visual results.[12,13] These therapies have dramatically improved the treatment of wAMD, providing opportunities for improving visual outcomes.[11]

Current Treatment Landscape

The current gold-standard treatment for wAMD is intravitreal anti-VEGF therapy.[11,14] For patients with wAMD, intravitreal anti-VEGF injections and monitoring is typically performed every 1–3 months, based on clinical response.[15] Frequent injections and high treatment burden create significant challenges for patients and providers. However, studies have demonstrated that visual outcomes are superior when patients are able to receive fixed treatments, as opposed to following an irregular dosing schedule.[16] Even with the most consistent and individualized treatment, visual loss may still result, related to such disease progression as atrophy or subretinal fibrosis.[19,20]

Future treatments of wAMD look toward increasing the longevity of the drug, resulting in less frequent injections (Table 1). Due to the nature of the administration of intravitreal anti-VEGF agents, blockade of VEGF is pulsatile. Should a longer-lasting drug be developed, vision outcomes may be more favorable, due to a continuous blockade of VEGF.[21] Furthermore, less frequent injections with longer drug efficacy will reduce the costs of antiangiogenic therapy for AMD.[11] This review outline current anti-VEGF treatments and ways by which their duration might be extended.

Current Therapies

Pegaptanib

Approved in 2004, 0.3 mg pegaptanib sodium (Macugen) reduced vision loss in neovascular AMD as an intravitreal injection at 6-week intervals compared to a sham molecule by targeting $VEGFA_{165}$.[22] It has largely become obsolete since its approval in 2004, as more effective anti-VEGF treatments have been introduced.

Bevacizumab

Initially approved for treating colon cancer, 1.25 mg bevacizumab (Avastin) has been used off-label since 2005 as a treatment for neovascular AMD.[23] It is a full-length, humanized, recombinant monoclonal antibody against all isoforms of VEGFA. It is significantly less expensive than many other anti-VEGF treatment options, as each vial can be fractionated into smaller doses for ocular use. Bevacizumab has been shown to be noninferior to ranibizumab in comparative studies, and is often used as a first-line agent.[24,45] Durability and drying efficacy of bevacizumab have been shown to be less than other agents in select patients.

Ranibizumab

Intravitreal 0.5 mg ranibizumab (Lucentis) was developed specifically for ocular use. It is a humanized, monoclonal antibody fragment that targets all isoforms of VEGFA.[17,18] Ranibizumab showed improvement in vision compared to a sham in the MARINA study and to photodynamic therapy in the ANCHOR study in predominantly classic lesions. Despite its promising clinical study results, real-world studies have been challenged to replicate the vision gain that patients experienced in the clinical studies of ranibizumab over the long term.[25,26,27,29]

Aflibercept

Aflibercept (2 mg), a recombinant fusion protein of specific domains from human VEGFR1, VEGFR2, IgG_1, was the first anti-VEGF agent to evaluate dosing with a more extended interval (eg, 8 weeks). It was approved in 2011, and is designed to target VEGFA, VEGFB, and PGF.[43]

Various studies have shown it to be noninferior to ranibizumab.[44]

Anti-VEGF Biosimilars

As bevacizumab, ranibizumab, and aflibercept have been available for over a decade, their patents have expired or are expiring shortly within the US and the European Union. This has allowed the development of anti-VEGF biosimilars: drugs that are similar to established treatments and mimic their effects, but do not have identical active ingredients in the way generic drugs do.[28] Anti-VEGF biosimilars must yield no differences in purity, efficacy, or safety from the established treatment to receive FDA approval. Currently, Mvasi (Amgen) and Zirabev (Pfizer) are available biosimilars for bevacizumab, and ONS-5010 (Outlook Therapeutics) is under development. Ranibizumab biosimilars under development include FYB201 (Formycon & Bioeq), Xlucane (Xbrane Biopharma), SB11 (Samsung Bioepis), PF582 (Pfenex), and Razumab (Intas Pharmaceuticals). While aflibercept is still within its patent life, anti-VEGF biosimilars like MYL1701 (Momenta Pharmaceuticals and Mylan NV), ALT-L9 (Alteogen), FYB203 (Formycon and Bioeq), and CHS2020 (Coherus Biosciences) are under development.[28]

Increasing Drug Longevity

Prolonging Drug Action

The distribution of a drug in the vitreous humour, which impacts durability, is affected by the drug's characteristics, including molecular weight/size, charge, protein-binding affinity, and the vitreous humor itself (eg, composition, volume).[30] This review includes a discussion of the importance of molecular size in prolonging treatment durability, as emphasized by several recent publications.[15,31,33]

Molecular Size and Dose

Molecular size has been central to the potential for increasing the effect of a specific dose. As limits exist in potential intravitreal volume of therapies (eg, 0.05 mL), drug durability is directly related to how much drug can be feasibly formulated into this volume. Smaller VEGF-binding molecules, such as brolucizumab (26 kDa), facilitate higher clinical doses than large VEGF-binding molecules, such as bevacizumab (149 kDa) or conbercept (143 kDa), while brolucizumab is available at 27.5-fold the dose of bevacizumab in an 0.05 intravitreal injection and 22-fold that of ranibizumab.[34] Brolucizumab was shown to be noninferior to aflibercept in the phase III trials HAWK and HARRIER and associated with enhanced fluid resolution in anatomic outcomes.[34] Molecular size plays a role not just in determining clinical dose but also in determining diffusion and clearance of the drug molecule from its compartment.[30]

The protein-binding affinity of an anti-VEGF agent has also been identified as an influence on drug efficacy. Affinity measures the strength of the interaction between the ligand (ie, the anti-VEGF agent) and the corresponding receptor (ie, VEGF). It can be measured through the equilibrium dissociation constant (K_d). Higher K_d values indicate weaker binding and lower affinity.[35] Of antibody-based anti-VEGF agents, bevacizumab, ranibizumab, and brolucizumab have been shown to have similar affinity for binding VEGF (1.6–58 pM).[30,36] VEGFR1/2 fusion proteins have been noted for their higher affinity and subpicomolar K_d values: aflibercept 0.49 pM, conbercept 6 pM, and the DARPin molecule abicipar pegol 2 pM.[30,37,38] While these drugs have high affinities, their clinical doses and equivalent molar doses will be important to consider in determining their durability, given their varying sizes (34–143 kDa).

Clearance and Half-Life

Increased duration of clinically relevant outcomes and subsequent reduced dosing frequency may be made possible through altering drug structure to reduce clearance and increase half-life.[30] Older eyes tend to show the process of liquefaction, or an increasing amount of vitreous humor that is liquid.[30] The vitreous (~4 mL in humans, 80% of the internal volume of the eye) consists in a suspension of water, hyaluronic acid, collagen, albumin, and other components that affects the diffusion and clearance of anti-VEGF molecules.[30] Following injection, anti-VEGF agents diffuse into the available volume in the posterior chamber, reach the retina and other ocular structures, where they bind to VEGF, and prevent the activation of VEGFR1.[39]

Used in pharmacokinetics to define the volume of plasma freed of a drug over time, "clearance" occurs as the concentration of a drug in the vitreous gradually decreases.[39] For the most part, large molecules are cleared through passive diffusion to the aqueous chamber into systemic circulation. Smaller, more lipophilic molecules may also be cleared at the retina–blood interface.[40, 41] Anti-VEGF agents are gradually cleared from the posterior chamber into systemic circulation after injection, rather than being subject to local metabolism or degradation.[30] Drug durability is related to its clearance, which

Table 1 Summary of Next-Generation Treatment Drugs

	Description	Advantages	Disadvantages	Status
0.5 mg conbercept	Recombinant human fusion protein of extracellular domains of VEGFR1, VEGFR2, and IgG_1 Fc	Significant increase in BVCA after 3 months compared to sham	No mean change in BVCA at 36 weeks with conbercept every 12 weeks compared to aflibercept every 8 weeks	Not FDA-approved, approved in China
6 mg brolucizumab	Single-chain antibody fragment	High molarity of drug may allow for more durability; noninferior to aflibercept; fluid resolution higher in brolucizumab group than aflibercept group	Concerns over inflammatory profile	FDA-approved
Abicipar pegol	Mono–designed ankyrin repeat protein	Longer half-life than ranibizumab (13 days vs 3 days, respectively); noninferior to ranibizumab	Relatively high rates of intraocular inflammation compared to ranibizumab	Received "complete response letter" from FDA
KSI-301	Anti-VEGF antibody–biopolymer conjugate	Large molar dose of drug allows for more durability; majority of patients able to go 6 months without retreatment after initial treatment in clinical trials	Efficacy and safety of longer-interval injections compared to aflibercept at 8-week intervals still under investigation	Not FDA-approved
Ranibizumab port-delivery system	Permanent, surgically implanted intraocular device	Nearly all patients in clinical trial able to go 6 months without medication refill after initial installation	Concerns over rates of vitreous hemorrhage	Not FDA-approved

contributes to its half-life (time it takes for drug concentration to decrease by half) within the vitreous.

Approximately five half-lives are required to eliminate 97% of a drug from a given system/compartment, as 50% of the drug is lost every half-life (ie, 50%, 75%, 87.5%, 93.75%, 96.875%). The clearance and apparent volume of drug distribution (V_{app}, ie, the vitreous cavity) is related to the half-life of a drug through the equation $t_{½} = \ln 2\ V_{app}/Cl_{total}$.[34] Half-life and clearance are inversely related: as clearance (Cl_{total}) of a drug decrease, its half-life increases. Current data for anti-VEGF agent intraocular half-lives are based on animal studies, as there are limited half-life data on anti-VEGF agents after intravitreal administration.[42] In rabbits, the vitreous half-life of aflibercept has been reported to be 3.63 days, while the vitreous half-life for ranibizumab was 3 days in primates and 2.88 in Dutch-belted rabbits.[21,30]

Given the lack of comprehensive data on ocular pharmacokinetics of anti-VEGF antibodies in humans after IVT injection, it is difficult to calculate the ideal frequency of administration, which is usually based on the half-life of the drug such that the appropriate concentration of the drug is sustained in the vitreous.[30] For now, then, dosage frequency of anti-VEGF agents is based on drug effect and a given individual's disease activity, rather than on the pharmacokinetics of these drugs.[30]

Next-Generation Therapeutics

Conbercept

A recombinant human fusion protein of extracellular domains of VEGFR1, VEGFR2, and a portion of Fc IgG_1, 0.5 mg conbercept (Lumitin; Chengdu Kanghong Pharmaceutical, Chengdu, Sichuan) varies from aflibercept with the addition of VEGFR2 domain 4, which allows for tighter binding to VEGFA, VEGFB, and PGF. In a phase III prospective, double-masked, multicenter, sham-controlled trial in neovascular AMD in China, the conbercept group showed a significant increase in BCVA compared to sham at 3 months.[46] After the primary outcome was reached at 3 months, the sham group crossed over. By 12 months, there was no significant difference in BCVA between the conbercept and sham groups.[46] The phase III trials PANDA-1 and PANDA-2 were randomized, quadruple-blinded, and multicentered with three equally distributed arms: 0.5 mg conbercept, 1 mg conbercept, and 2 mg

aflibercept. The study failed to meet its primary end point of mean change in BVCA at 36 weeks with conbercept every 12 weeks compared to aflibercept every 8 weeks.[47]

Brolucizumab

Approved in 2019,[32] 6 mg brolucizumab (Beovu; Novartis Logo, Basel) is a new anti-VEGF agent that targets VEGFA.[3] It is a single-chain antibody fragment, and its small dimensions allow for a very high molar concentration in a 0.05 mL injection, which may have a positive impact on its durability.[43,48] In the HAWK and HARRIER trials it was shown to be noninferior to aflibercept at 8 and 12-week intervals.[34,49] A significant number of patients were maintained on a 12-week interval for treatments, with >50% of patients at the 48-week period in both the HAWK and HARRIER trials, and >75% maintained at the 12-week interval by 96 weeks.[34] Fluid resolution appeared to be more robust for brolucizumab than aflibercept. Despite these promising initial results, there is concern over the inflammatory profile of the drug, with intraocular inflammation, such as retinal vasculitis and retinal occlusive vasculitis, occurring in some patients.[50]

Abicipar Pegol

Targeting all isoforms of VEGF, abicipar pegol (Abicipar; Allergan, Coolock, Dublin) is a mono–designed ankyrin repeat protein (mono-DARPin).[51] DARPin is a 14 kDa recombinant protein, 34 kDa when covalently linked to a 20 kDa polyethylene glycol tail to increase molecular size, allowing the drug to be administered at longer intervals.[52] The drug's relatively long vitreous half-life of 13 days is significantly more than ranibizumab's half-life of approximately 3 days.[30] Abicipar injections every 8 and 12 weeks were found to be noninferior to ranibizumab injections given every 4 weeks in the CEDAR and SEQUOIA studies.[51] However, the abicipar group demonstrated intraocular inflammation at a rate of 15.4% compared to only 0.3% intraocular inflammation following ranibizumab injection.[13] Following manufacturing changes, the rate of inflammation decreased to 8.9% in the MAPLE study. Given the rates of inflammation, the FDA did not initially approve abicipar and instead delivered a "complete response letter."[49]

KSI-301

KSI-301 (Kodiak Sciences, Palo Alto, CA) is an anti-VEGF antibody–biopolymer conjugate comprised of a humanized anti-VEGF antibody (similar to ranibizumab) and an ultra–high molecular weight phosphorylcholine-based polymer, which increases intraocular stability and drug durability.[13] KSI-301 is an example of leveraging molecular weight to increase drug longevity and reduce the frequency of intravitreal injections. With a molecular weight of 950 kDa, it is by far the largest anti-VEGF drug.[31] Its size and clinical dose (5 mg, or an equivalent dose of 3.5 M) creates an equivalent molar dose seven times that of ranibizumab (48 kDa, equivalent dose 0.5 M).[15,53] In a phase IB, randomized, open-label study with KSI-301 (utilizing both 2.5 mg and 5.0 mg clinical doses) targeting patients with neovascular AMD, diabetic macular edema, and retinal vein occlusion, 55% of patients enrolled in the neovascular AMD branch went 6 months without retreatment. After retreatment, 84% of patients were able to go 4 months without additional treatment, which may indicate KSI-301's ability to significantly decrease the treatment burden felt by many patients with wAMD.[31] Currently, DAZZLE (NCT04049266), a phase IIB/III study is recruiting to investigate the efficacy and safety of repeated KSI-301 injections in 368 patients with wAMD given at 12-, 16-, or 20-week intervals following an initial three loading doses, while being compared to aflibercept at 8-week intervals following the three initial monthly loading doses.[54]

Ranibizumab Port-Delivery System

The ranibizumab port-delivery system (PDS; Genentech) is a permanent, surgically implanted intraocular device that allows for clinic-based refills.[55,56] Containing a high-concentration ranibizumab formulation (up to 100 mg/mL) that slowly diffuses into the vitreous, the ranibizumabPDS is designed to continuously release ranibizumab directly into the vitreous cavity at appropriate intervals and extend treatment duration.[57] In the phase II LADDER trial, the ranibizumab PDS gave comparable visual and anatomic results to traditional intravitreal injections.[56] The phase III trial ARCHWAY has shown noninferior outcomes and equivalent visual acuity with the use of the 100 mg/mL surgical implant compared to monthly ranibizumab injections, and 98% of patients were able to last 6 months on the PDS without a medication refill.[58] The ARCHWAY trial is being continued in the ongoing PORTAL study. Currently, there are concerns over rates of vitreous hemorrhage, and the delivery technique is being altered.[59]

Conclusion

Neovascular AMD may lead to devastating effects on patients' vision, lifestyle, and independence. Its complex pathogenesis has led to the development of several treatment options, the most common of which has traditionally been the use of anti-VEGF agents to block the VEGF pathway. Currently, these anti-VEGF agents require frequent intravitreal injections, making treatment difficult to sustain, which may limit long-term visual outcomes.

A major focus for future wAMD therapeutics is extending drug durability to limit treatment frequency and reduce office visits, lessening the barriers to treatment. Decreasing molecular size is one avenue of increasing the dose of an anti-VEGF agent, as seen in trials of brolucizumab. Alteration of binding affinity (as in the case of VEGFR-fusion proteins, such as aflibercept and conbercept) may allow for reduced clearance of the drug, increasing its longevity. Developing drugs with longer half-lives is also an area of interest, such as with KSI-301 and abicipar pegol, which have given promising results in extended doses. Finally, forgoing traditional injections altogether in favor of alternative delivery methods, such as the ranibizumab PDS, may allow for a more sustained treatment model. The advent of anti-VEGF therapy has been a game changer for our patients with wAMD. The next phase for enhancing patient outcomes will likely come through improved durability and decreased treatment burden. Ongoing clinical trials and multiple emerging therapeutics provide an exciting landscape to watch as the future for treatment of this impactful disease continues to evolve.

Funding

This work was supported by the Heed Ophthalmic Foundation Award to Sruthi Arepalli, MD.

Disclosure

Justis P Ehlers reports grants from Novartis, Alcon, Oxurion, Aerpio, Regeneron, Genentech, Boehringer-Ingelheim, and Roche, consulting fees from Novartis, Alcon, Adverum, Allergan, Thrombogenics, Aerpio, Stealth, Regeneron, Allegro, and Zeiss, and patents/intellectual property/licensing with Bioptigen/Leica outside the submitted work. The authors report no other conflicts of interest in this work.

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