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REVIEW



Emerging vascular endothelial growth factor antagonists to treat neovascular age-related macular degeneration

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ABSTRACT

Introduction: Evolving anti-vascular endothelial growth factor (VEGF) treatments for neovascular age-related macular degeneration (nAMD) include long acting agents, combination strategies involving new pathways, topical agents, sustained-release, and genetic therapy strategies.

Areas covered: Brolucizumab and abicipar pegol have smaller molecular size, facilitating higher concentrations and potentially longer duration than current anti-VEGF agents. Agents being combined with anti-VEGFs include OPT-302 (to inhibit VEGF-C and VEGF-D); pegpleranib and rinucumab (to inhibit platelet derived growth factor, PDGF – but both failed to show consistently improved visual outcomes compared to anti-VEGF monotherapy); and RG7716, ARP-1536 and nesvacumab (to activate the Tie-2 tyrosine kinase receptor, which reduces permeability). X-82 is an oral anti-VEGF and anti-PDGF being tested in phase 2 studies. Topical anti-VEGF ± anti-PDGF drugs under study include pazopanib, PAN-90806, squalamine lactate, regorafenib, and LHA510. Sustained-release anti-VEGF delivery treatments, such as the ranibizumab Port Delivery System, GB-102, NT-503, hydrogel depot, Durasert, and ENV1305 aim to reduce the burden of frequent injections. Gene therapies with new viral vectors hold the potential to induce sustained expression of anti-angiogenic proteins via the retina's cellular apparatus, and include AVA-101/201, ADVM-202/302, AAV2-sFLT01, RGX314, and Retinostat.

Expert opinion: There are many emerging anti-VEGF treatments that aim to improve visual outcomes and reduce the treatment burden of nAMD.

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1. Background

Age-related macular degeneration (AMD) is the leading cause of irreversible legal blindness in people ≥ 65 years of age in the Western world, affecting over 1.7 million people in the United States and expected to reach almost 3 million by 2020 [1]. In the United Kingdom, the prevalence of advanced-stage AMD in patients ≥ 50 years of age is 2.4%, with an estimation of 679,000 cases by 2020 [2]. This disease is characterized by progressive degenerative abnormalities in the macula of the eye, the central portion of the retina responsible for fine vision. AMD is classified into one of two general subgroups: the non-neovascular (non-exudative or dry) form of the disease and the neovascular (exudative or wet) form of the disease. The non-neovascular form of AMD accounts for approximately 90% of all AMD cases and is often characterized by a slow degeneration of the macula, resulting in atrophy of the central macula with gradual vision loss over a period of years. In contrast, neovascular AMD (nAMD), although less prevalent, commonly causes sudden and often substantial loss of central vision, accounting for most cases of severe vision loss in this disease. This type of AMD is characterized by the growth of pathologic choroidal neovascularization (CNV) beneath the macula, which causes exudation of blood and/or fluid into the macula. Ultimately, neovascular tissue

and associated exudates develop into a destructive macular scar, leading to central blindness.

The aberrant vascular growth and exudation in nAMD are driven by upregulation of one of the main cytokines involved in angiogenesis, vascular endothelial growth factor-A (VEGF-A). This cytokine is also one of the most potent inducers of permeability and was, in fact, originally called vascular permeability factor [3]. The introduction of intravitreally administered anti-VEGF-A agents has led to notably improved outcomes for patients with nAMD. In clinical trials, these outcomes are assessed using Best-Corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity (VA) measurement, which involves protocol-specified refraction, and represents a well-established method of functional assessment of vision.

2. Medical need

Despite the impressive advancements in nAMD treatment over the past two decades, there are several practical limitations to anti-VEGF-A therapy, including the high cost of certain agents, need for frequent intravitreal injections, incomplete response, and/or failure to maintain response in some patients. Even with regularly repeated dosing of anti-VEGF therapy over 1 year, approximately 20% of patients lose vision, approximately 50% do not achieve 20/40 VA (which is necessary for an unrestricted driver's license in

Table 1. Summary of currently available intravitreal anti-VEGF therapies.

Anti-VEGF agents	Description	FDA approval date/indication
Macugen (pegaptanib) 0.3 mg/0.05 ml	Pegylated synthetic RNA-based oligonucleotide targeting VEGF ₁₆₅	17 December 2004/nAMD
Avastin (bevacizumab) 1.25 mg/0.05 ml	Recombinant humanized monoclonal IgG1 antibody against VEGF	Approved on 24 February 2004 for metastatic colorectal cancer; used off-label for nAMD since 2005.
Lucentis (ranibizumab) 0.5 mg/0.05 ml	Humanized IgG1 antibody fragment against VEGF	30 June 2006/nAMD
Eylea (aflibercept) 2 mg/0.05 ml	VEGF-trap, a recombinant protein created by fusing the second Ig domain of human VEGF receptor 1 with the third domain of human VEGF receptor 2, which in turn is fused to the constant region of human IgG1	18 November 2011/nAMD

RNA: ribonucleic acid; VEGF: vascular endothelial growth factor; nAMD: neovascular age-related macular degeneration; IgG1: immunoglobulin G1.

regions of the United States and in most European Union countries), and 2/3 or more do not achieve a VA gain of 3 or more ETDRS lines [4,5].

Although one recent international database observational study showed that favorable visual outcomes could be obtained with aflibercept dosed in a treat and extend manner [6], 'real-world' outcomes of anti-VEGF-A therapy are generally worse than those obtained in clinical trials, potentially due to undertreatment [7]. For example, a large retrospective medical database claims analysis in the USA showed that 19,000 newly diagnosed nAMD patients received a mean of 4.6 and 6.9 injections of bevacizumab and ranibizumab over 12 months, respectively. A meta-analysis of anti-VEGF-A treatment regimens for nAMD suggests that there is a positive linear correlation with VA gains and number of injections over 12 months, although there was a ceiling effect, in which over 9 injections annually did not result in further gains [8]. There are many barriers that pose a challenge to patient compliance with frequent anti-VEGF-A injection, such as patient anxiety/discomfort, financial burden, time constraints, and lack of transportation [9]. Due to these barriers, there is great interest in development of long-acting anti-VEGF formulations.

Although anti-VEGF-A therapies initially improve vision by reducing leakage from neovascularization during the first months of treatment, they have limited ability to cause regression of this pathologic submacular neovascularization. Ultimately, the formation of submacular scar limits further visual benefit despite treatment; a recent large randomized controlled study showed that submacular scar develops in nearly 50% of subjects despite 2 years of anti-VEGF-A treatment [10]. For those patients with incomplete response to anti-VEGF-A therapy, there is great interest in targeting other pathways involved in angiogenesis.

3. Existing treatment

3.1. Previous nAMD treatments

Prior to the advent of anti-VEGF-A therapy, nAMD was treated with focal laser therapy, intravitreal steroids, photodynamic therapy with verteporfin, and surgical excision of choroidal neovascular membranes. These treatments did not significantly improve vision and thus are not used frequently today [9]. The four currently available anti-VEGF agents are described below and summarized in Table 1.

3.2. Pegaptanib

In 2004, pegaptanib sodium (Macugen®, Bausch and Lomb), an aptamer designed to target the 165 isoform of VEGF-A, was the first of its class agent approved for the treatment of nAMD. Registration studies (VISION-1) showed that subjects receiving intravitreal 0.3 mg pegaptanib every 6 weeks for 1 year experienced approximately half the vision loss as those subjects who received sham [11]. Pegaptanib use has fallen out of favor since more effective anti-VEGF-A agents have become available.

3.3. Ranibizumab

Ranibizumab (Lucentis®, Roche/Genentech), a smaller recombinant humanized monoclonal antibody fragment targeting VEGF-A, was specifically manufactured for use in the eye, and inhibits all known isoforms of VEGF-A. This molecule lacks a fragment crystallizable (Fc) region, which allows for faster systemic clearance [12]. In the MARINA and ANCHOR registration trials involving monthly ranibizumab, nAMD subjects experienced a mean improvement in vision acuity of 7.2 and 11.3 ETDRS letters respectively at 1 year, compared to a mean loss of 10.4 and 9.5 ETDRS letters in the sham and Verteporfin control groups, respectively [4,13]. Ranibizumab 0.5 mg was approved for the treatment of nAMD in 2006.

3.4. Bevacizumab

Bevacizumab (Avastin®, Roche/Genentech) is a full-length recombinant humanized monoclonal anti-VEGF that binds all isoforms of VEGF-A [14]. It was originally approved for the treatment of metastatic colorectal cancer, but was used off-label in 2005 for the treatment of exudative AMD. It is the least costly anti-VEGF-A option [15] and hence the first option considered for many patients. Off-label bevacizumab 1.25 mg was found to be non-inferior to ranibizumab in the Comparison of AMD Treatments Trials (CATT, a National Institutes of Health sponsored study) [13] and the analogous IVAN Study performed in the United Kingdom [16].

3.5. Aflibercept and ziv-aflibercept

Aflibercept (Eylea®, Regeneron) is a recombinant fusion protein that is composed of human VEGF Receptor-1 and VEGF Receptor-2 fused to the Fc domain of human immunoglobulin G1 domain. It inhibits VEGF-A, VEGF-B, and placental growth

factor (PLGF), another member of the VEGF subfamily [14]. In 2011, aflibercept 2 mg (also known as VEGF Trap-EYE) was approved for the treatment of nAMD after various regimens in the VIEW-1 and VIEW-2 studies were shown to be noninferior to monthly ranibizumab over a 1-year time period [5]. It can be dosed every 8 weeks following three monthly loading doses, which offers the benefit of less frequent office visits compared to ranibizumab and bevacizumab.

In oncology, aflibercept is FDA-approved chemotherapy for metastatic colorectal cancer and is known as ziv-aflibercept or Zaltrap® (Regeneron). Ziv-aflibercept has an identical chemical structure as aflibercept, although the osmolality of ziv-aflibercept is 1000 mOsm/kg compared to 300 mOsm/mg for aflibercept, due to the addition of sucrose. Ziv-aflibercept can be compounded for intravitreal injection at a cost comparable to bevacizumab (in US dollars, approximately \$50 vs. nearly \$2000 for aflibercept). In one study, monthly intravitreal injection of off-label ziv-aflibercept in patients with nAMD improved anatomic and visual outcomes without evidence of ocular toxicity when followed for 3 months [17]. In another study, as needed treatment with ziv-aflibercept can increase the treatment-free interval while maintaining 12-month visual and anatomic outcomes in nAMD patients that are nonresponders to ranibizumab or bevacizumab [18].

4. Market review

The market to treat nAMD in seven major countries (USA, UK, Japan, Italy, Spain, France, and Germany) was valued at \$5.1 billion (\$ = US dollar throughout this manuscript) in 2013 and is expected to double to \$10.1 billion in 2023 [19]. The compound annual growth rate of 7.1% is driven by the aging population with increased incidence of nAMD, along with expanding treatment options to manage this chronic disease. Anti-VEGF-A drugs, such as bevacizumab, ranibizumab, and aflibercept, account for 98% of the total treatment sales in managing AMD.

In the USA, off-label bevacizumab is the most commonly initiated treatment due to its price of approximately \$50 per injection, compared to approximately \$2000 for ranibizumab and \$1850 for aflibercept. In Europe, the costs of bevacizumab, ranibizumab, and aflibercept are roughly € 70, € 700, and € 600 (approximately \$78, \$784, and \$672, respectively) per injection respectively, which represents a significant discount in price for ranibizumab and aflibercept compared to the USA [20]. Bevacizumab is estimated to hold approximately 60% of the USA wet AMD market by volume [21]. A survey in the UK revealed that bevacizumab only accounted for 3% of anti-VEGF-A injections administered in January 2015, likely due to concerns about its off-label status [22]. In 2015, aflibercept surpassed ranibizumab as the highest selling FDA-approved intravitreal anti-VEGF-A drug. According to a press release from Regeneron, aflibercept's sales in the USA in 2016 were valued at \$3.32 billion, which is a 24% increase compared to sales in 2015 [23]. In contrast, 2016 sales of ranibizumab in the USA dropped 10% compared to 2015, with sales of 1.41 billion Swiss francs (approximately \$1.45 billion) according to a publicly available investor update from Roche [24].

5. Current research goals

Given the limitations of anti-VEGF-A therapy, along with burdensome need for repeated intravitreal injections to sustain efficacy, alternate treatment modalities are being developed. Anti-platelet-derived growth factor (anti-PDGF) therapy has been an area of immense research focus, as several companies have developed drugs in this class with the intent to combine them with anti-VEGF-A therapy. Other new drugs modulate the Tie-2 receptor kinase, which when activated, reduces vascular permeability. The desire to reduce injection frequency has led to the development of sustained-release formulations of anti-VEGF drugs, along with topical and oral formulations. Gene therapy with viral vectors holds the potential to induce continuous expression of therapeutic anti-angiogenic proteins in the eye with one treatment.

6. Scientific rationale for anti-VEGF-A monotherapy and combination therapies

6.1. The role of VEGF

VEGF plays a key role in both angiogenesis and vascular permeability [25]. There are several different members of the VEGF family including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E, and PLGF. The actions of VEGF family members are mediated by the activation of tyrosine kinase receptors. The VEGF receptors (VEGFR) have seven immunoglobulin-like loops in their extracellular domain and a kinase insert region in the intracellular domain. VEGFRs can signal via mitogen-activating protein kinase signaling pathway or through elevation in intracellular calcium concentration in endothelial cells forming the vessel walls [26].

VEGF-A includes several isoforms due to alternate mRNA splicing and is a critical regulator of ocular angiogenesis and vascular permeability. VEGF-A acts at VEGFR 1 and 2. VEGFR1 has both positive and negative angiogenic effects; VEGFR2 is the primary mediator of the mitogenic, angiogenic, and vascular permeability effects of VEGF-A [25]. VEGF-A mediates angiogenesis by promoting endothelial cell migration, proliferation, and survival [27]. VEGF-A also possesses inflammatory properties through its capacity to mediate microvascular permeability and increase adhesion of leukocytes [28].

6.2. The role of PDGF

Several studies suggest that limitations of anti-VEGF-A therapy may be related to pericytes [29–31]. Pericytes are mesenchymal cells that share a common basement membrane with endothelial cells, effectively covering them, while also providing VEGF-A and other growth factors via paracrine signaling [32,33]. Consequently, the neovascular endothelial cells may be protected in the setting of anti-VEGF-A therapy, promoting resistance to anti-VEGF-A agents. PDGF mediates the recruitment, maturation, and survival of pericytes [34]; hence, anti-PDGF therapy is aimed at stripping pericytes in order to increase the potency of anti-VEGF-A therapy. Furthermore, PDGF may be involved in subretinal fibrosis, and anti-PDGF therapy could decrease this cause of permanent vision loss in nAMD.

6.3. The role of the Tie-2 receptor

Another target of interest in treating exudative vascular diseases of the retina is the Tie-2 tyrosine kinase receptor, which is expressed on endothelial cells. Tie-2 receptor activation results in reinforcement of junctional proteins and stabilization of vasculature to limit permeability [35]. Angiopoietin-1 (Ang-1) is a ligand that activates the Tie-2 receptor, thereby limiting vascular leakage. Angiopoietin-2 (Ang-2) is a competitive antagonist to Ang-1, and hence elevated Ang-2 levels cause increased vascular leakage [36]. Several new drugs have been designed to inhibit Ang-2, thus allowing more Ang-1 to activate the Tie-2 receptor, resulting in anti-permeability effects. Another approach centers on the enzyme, vascular endothelial protein tyrosine phosphatase (VE-PTP), which inactivates the Tie-2 receptor. One therapy under development inhibits VE-PTP, thus preventing inactivation of the Tie-2 receptor, to stabilize vasculature and limit leakage.

7. Competitive environment

7.1. Future anti-VEGF medications

See Table 2 for a summary of all the anti-VEGF-A medications in development.

7.1.1. Brolucizumab

Brolucizumab (Novartis) is a humanized single-chain antibody fragment inhibitor of VEGF-A that has a smaller molecular weight (26 kDa) compared to aflibercept (115 kDa) and ranibizumab (48 kDa). Its molecular properties allow a higher molar concentration to be prepared in a 0.05 ml intravitreal

injection, which may allow for an extended duration of effect, lower systemic exposure, and improved ocular tissue penetration. A phase 1/2 study showed that a single injection of brolucizumab given in 4.5 and 6.0 mg doses was noninferior in central subfield thickness (margin: 40 μ m) at 1 month end-point compared to ranibizumab 0.5 mg. The median time to post-baseline therapy for the brolucizumab 6.0 mg dose was 75 days, a 30-day increase compared to ranibizumab 0.5 mg. The safety profile of brolucizumab was consistent with that of other intravitreal anti-VEGF-A drugs [37].

The phase 2 OSPREY trial demonstrated that brolucizumab 6 mg injection every 8 weeks was well-tolerated and noninferior compared to aflibercept 2 mg injection every 8 weeks [38]. Patients treated with brolucizumab gained 5.8 and 6.0 letters at the 12 week and 16 week marks, compared to 6.9 and 6.6 letters in the aflibercept group. The brolucizumab group had more stable central subfield thickness reduction, fewer unscheduled treatments (6 vs. 15), and higher rates of fluid resolution. The brolucizumab group was switched to a 12-week injection interval from weeks 36 to 56, and 18 of 39 eyes (46%) had stable BCVA and did not require unscheduled injection [39].

Based on the results of the previous studies, the phase 3 HAWK and HARRIER trials (NCT02307682, NCT02434328) compared aflibercept 2.0 mg to brolucizumab 3.0 mg and brolucizumab 6.0 mg. This study enrolled 1800 patients across 400 centers worldwide. After 3 monthly loading doses, the brolucizumab groups were treated every 12 weeks, with the option of switching to 8-week dosing in case of recurrent disease activity [40]. A Novartis press release from June 2017 announced that the brolucizumab

Table 2. Summary of emerging drugs to treat neovascular age-related macular degeneration (nAMD).

Compound	Company	Stage of development	Structure/mechanism of action
Brolucizumab	Novartis	Phase 3 completed	Small MW humanized single-chain Fab anti-VEGF-A
Abicipar pegol	Allergan	Phase 3	DARPin antagonist of VEGF-A
OPT-302	Ophthea	Phase 2b scheduled for 2017	Anti-VEGF-C/VEGF-D
Pegpleranib (Fovista)	Ophthotech	Phase 3 did not meet end point	Anti-PDGF-B aptamer
Rinucumab-aflibercept	Regeneron	Phase 2 did not meet end point	Anti-PDGF-B/anti-VEGF co-formulation
DE-120	Santen	Phase 2	Dual TKI of VEGF-A/PDGF
Nesvacumab-aflibercept	Regeneron	Phase 2	Ang-2/VEGF-A mAb co-formulation
RG7716	Roche	Phase 2	Bispecific Ang-2/VEGF-A antibody
ARP-1536	Aerpio	Preclinical	Tie-2 receptor activation (via VE-PTP inhibition)
X-82	Tyrogenex	Phase 2	Oral anti-VEGF-A/PDGR
Pazopanib	GlaxoSmithKline	Phase 2b results (2015)	TKI of VEGF-A/PDGF
PAN-90806	PanOptica	Phase 1/2	TKI of VEGF-A/PDGF
Squalamine lactate	Ohr Pharmaceuticals	Phase 3 suspended enrollment	TKI of VEGF-A/PDGF/bFGF
Regorafenib	Bayer Healthcare	Phase 2a did not meet end point	TKI of VEGF-A/PDGF
LHA510	Alcon	Phase 2	VEGF-A inhibitor
Ranibizumab PDS	Genentech	Phase 2	Refillable port of VEGF-A mAb
GB-102	GrayBug Vision	Preclinical	Bioerodible nanoparticles encapsulate TKI of VEGFR/PDGR
NT-503 ECT	Neurotech	Phase 2 terminated	VEGF-A receptor fusion protein
Hydrogel depot	Ocular Therapeutix	Preclinical	Sustained release anti-VEGF-A
Durasert	pSivida	Preclinical	TKI of VEGF-A/PDGF
ENV1305	Envisia Therapeutics	Preclinical	Sustained release anti-VEGF-A
AVA-101	Avalanche Biotechnologies	Phase 2a results were mixed	AAV sFLT
ADVM-022 & ADVM-032	Adverum Biotechnologies	Preclinical	AAV encoding anti-VEGF-A (aflibercept & ranibizumab respectively)
AAV2-sFLT01	Genzyme (Sanofi)	Phase 1	AAV sFLT
RGX-314	Regenxbio	Preclinical	AAV8 encoding anti-VEGF-A
Retinostat	Oxford Biomedica	Phase 1	EIAV encoding endostatin and angiostatin

MW: molecular weight; Fab: fragment antibody; VEGF: vascular endothelial growth factor; DARPin: designed ankyrin repeat protein; PDGF: platelet-derived growth factor; TKI: tyrosine kinase inhibitor; Ang-2: angiopoietin-2; mAb: monoclonal antibody; VE-PTP: vascular endothelial-protein tyrosine phosphatase; PDGR: platelet-derived growth factor receptor; bFGF: beta fibroblast growth factor; VEGFR: vascular endothelial growth factor receptor; AAV: adeno-associated virus; sFLT: soluble fms-like tyrosine-kinase 1; cDNA: complementary deoxyribonucleic acid.

6.0 mg group met the primary endpoint of noninferiority compared to aflibercept every 8 weeks (measured by mean change in BCVA from baseline to week 48). A majority of patients, 57% (HAWK) and 52% (HARRIER), were maintained exclusively on a 12-week interval immediately following the 3-month loading phase through week 48. The mean number of brolucizumab and aflibercept injections administered throughout the 48-week study period were not specified. The rates of ocular and non-ocular adverse events were comparable between aflibercept and brolucizumab [41].

7.1.2. Abicipar pegol

Abicipar pegol (Allergan and Molecular Partners) is a monoDARPin (designed ankyrin repeat protein) that blocks all isoforms of VEGF-A. The Phase 2b trial data (accessible from the Allergan and Molecular Partners websites) indicate that it has more potent VEGF-A inhibition, smaller molecular size (34kDa), and longer duration (12 weeks) than the currently available anti-VEGF-A agents. Abicipar 2.0 mg given every 4 weeks for three loading doses outperformed ranibizumab 0.5 mg given every 4 weeks. At 20 week follow-up, the abicipar group gained a mean of 9.0 letters (although sham injections were administered after week 8), while the ranibizumab group gained only 4.7 letters with continued monthly dosing [42].

In this phase 2b study, approximately 10% of patients who received abicipar experienced ocular inflammation episodes [43]. Allergan has worked to improve the abicipar formulation and purification process with the intent to reduce the incidence of inflammation in phase 3 trials. Similar problems with inflammation were encountered with ranibizumab during early clinical trials, which were successfully resolved in later trials. The abicipar phase 3 trials (NCT02462486) will compare treatment arms of abicipar given every 8 weeks (duration equal to aflibercept), abicipar every 12 weeks (duration superior to aflibercept), and ranibizumab given every 4 weeks [44].

7.1.3. OPT-302

OPT-302 (Opthea), targets VEGF-C and VEGF-D, which may play a role in anti-VEGF-A therapy. A phase 1 study (NCT02543229) showed that in treatment-naïve patients, combination therapy of OPT-302 and ranibizumab intravitreal injections administered every 4 weeks resulted in meaningful additional VA gain and reduction in macular thickness compared to ranibizumab alone at 12 week follow-up. In previously treated patients that were poor responders to anti-VEGF-A therapy, there were improved outcomes with addition of OPT-302, suggesting additional benefit of VEGF-C and VEGF-D inhibition [45]. Phase 2B trials are scheduled to commence in 2017.

7.2. Anti-VEGF plus anti-PDGF combination therapy

As noted above, pericytes may play a role in limiting the efficacy of anti-VEGF-A therapy. Consequently, combinations of anti-PDGF therapies, which target pericytes, and anti-VEGF-A therapies could provide enhanced efficacy over anti-VEGF-A mono-therapy.

7.2.1. Pegpleranib

Pegpleranib (Fovista®, Ophthotech) is 32-mer pegylated DNA aptamer that selectively binds to PDGF-BB homodimers and PDGF-AB heterodimers to prevent their binding with PDGF tyrosine kinase receptors expressed on pericytes. It is administered as a separate intravitreal injection in combination with intravitreal anti-VEGF-A therapy. The phase 2b study enrolled 449 treatment-naïve patients with nAMD to one of three intravitreal treatment arms every month: pegpleranib 0.3 mg plus ranibizumab 0.5 mg, pegpleranib 1.5 mg plus ranibizumab 0.5 mg, and sham plus ranibizumab 0.5 mg. Pegpleranib was well tolerated and demonstrated a dose-dependent relationship. The 1.5 mg combination therapy regimen outperformed ranibizumab monotherapy, with a mean gain of 10.6 ETDRS letters compared to 6.5 letters at 24 week follow-up, respectively [46].

An Ophthotech press release revealed that phase 3 trials (NCT01944839) of pegpleranib-ranibizumab combination therapy did not duplicate the success of the phase 2b trial. Analyses of the Year-1 data from two of the three phase 3 trials indicated that the addition of pegpleranib to the monthly ranibizumab regimen did not result in increased visual benefit [47,48]. The results from the third phase 3 trial are due in the latter half of 2017.

7.2.2. Rinucumab

Rinucumab (Regeneron) is an anti-PDGF receptor- β antibody. It has been co-formulated with aflibercept for a single injection that was studied in the phase 2 CAPELLA trial (NCT02418754). At 12-week follow-up, rinucumab/aflibercept failed to meet its primary endpoint of improved BCVA compared to aflibercept alone. It also failed to show additional benefit in reduction of retinal thickness compared to aflibercept alone [48,49].

7.2.3. DE-120

A third anti-PDGF agent, DE-120 (Santen Pharmaceuticals), is currently under study in Phase 2 trials (NCT02401945). It is a small molecule dual tyrosine kinase receptor inhibitor (TKI) of VEGF-A and PDGF that is delivered by intravitreal injection [50].

7.2.4. X-82

X-82 (Tyrogenex) is an oral anti-PDGF and VEGF-A inhibitor. In the Phase 1 dose-escalation study (NCT02348359), 10 of 35 patients (29%) did not complete the 24-week endpoint, with six (17%) withdrawing due to adverse events. The most common adverse events were diarrhea ($n = 6$), nausea ($n = 5$), fatigue ($n = 5$), and elevated transaminase enzymes ($n = 4$) that reversed with cessation of X-82. 24 of the 25 patients that completed the 24-week trial maintained or improved their VA (mean +3.8 letters), and 15 of 25 (60%) did so without need for rescue ranibizumab injections (as specified by predefined retreatment criteria). Mean central subfield thickness was reduced by a mean of 50 μ m, and eight patients (all receiving at least 100 mg daily dose) maintained sustained reductions without need for rescue ranibizumab injection [51]. The Phase 2 APEX study (NCT02348359) is comparing X-82 with as-needed aflibercept injections to aflibercept monotherapy.

7.3. Anti-VEGF-*a* plus tie-2 receptor modulator combination therapy

As noted above, activation of the Tie-2 receptor stabilizes vasculature and limits permeability. Consequently, modulating the Tie-2 receptor in combination with anti-VEGF-A therapy may provide enhanced efficacy over anti-VEGF-A monotherapy.

7.3.1. Nesvacumab

Nesvacumab (Regeneron) is an Ang-2 inhibitor, that when combined with aflibercept, may increase the duration of aflibercept's anti-permeability effects. Nesvacumab-aflibercept was well tolerated by 20 patients in a phase 1 trial sponsored by Regeneron. VA and anatomical improvements at all dose levels were encouraging [52,53]. The phase 2 ONYX study (NCT02713204) is currently ongoing [54].

7.3.2. RG7716

RG7716 (Roche) is a bispecific crossed monoclonal antibody that binds VEGF-A and Ang-2 to treat nAMD [55]. A bispecific monoclonal antibody could theoretically provide benefit over co-formulations of two separate antibodies, as the higher necessary concentrations of protein in a co-formulation can cause protein aggregation and inactivation.

The phase 1 study of RG7716 (NCT01941082) demonstrated that it was well tolerated in a population of suboptimal responders to anti-VEGF-A therapy, who had been diagnosed with nAMD for over 2 years. Patients received RG7716 every 4 weeks for a total of three doses. In the highest dose (6 mg) group, patients gained a median of 7.5 letters and had a reduction in macular thickness of 117 μ m 28 days after the last administration. Based on these positive results, the phase 2b AVENUE study (NCT02484690) is underway to test RG7716's efficacy in a larger population [56].

7.3.3. ARP-1536

ARP-1536 (Aerpio Therapeutics) is a novel monoclonal antibody that activates the Tie-2 receptor by an alternative pathway. As noted above, VE-PTP is the most downstream negative regulator of Tie-2, which is not addressed by other drugs in the pipeline. ARP-1536 is administered by intravitreal injection and binds to the extracellular domain of VE-PTP, inhibiting it, and thus causing increased activation of the Tie-2 receptor. Preclinical studies have established biologic activity similar to AKB-9778, Aerpio's other VE-PTP inhibitor that is administered by subcutaneous injection and has been assessed in the phase 2 TIME-2 study (NCT02050828) of diabetic macular edema [57].

7.4. Topical treatments

7.4.1. Pazopanib

Pazopanib (GlaxoSmithKline) is a topical VEGF-A TKI that inhibits both VEGF-A and PDGF. Phase 2b trial results were released in 2015. In a 510 patient study, at the 52 week endpoint, Pazopanib QID combined with as-needed ranibizumab was found to be noninferior to ranibizumab dosed as-needed or monthly; however, the addition of pazopanib did not decrease the number of as-needed ranibizumab injections by

>50% (the prespecified minimum criterion of efficacy). There was no significant difference in retinal thickness and size of lesion between groups [58].

7.4.2. PAN-90806

PAN-90806 (PanOptica), another VEGF-A inhibitor eyedrop, has been shown to produce an anti-VEGF-A response comparable to currently available anti-VEGF-A therapies in half of 50 treatment naïve nAMD patients, according to a phase 1/2 study (NCT02022540) presented at the 2016 American Academy of Ophthalmology Retina Subspecialty Day. PanOptica plans to initiate a phase 1/2 clinical trial of an updated formulation for patients with nAMD in 2017. This newer suspension was designed to reduce the incidence of punctate keratopathy as a side effect [59].

7.4.3. Squalamine lactate

Squalamine lactate eyedrops (Ohr Pharmaceutical) prevent downstream signaling of multiple angiogenic factors (VEGF Receptor-1, VEGF Receptor-2, PDGF Receptor, and b-FGF-Receptor). The phase 2 IMPACT study (NCT02511613) compared squalamine drops BID plus ranibizumab as needed with placebo plus ranibizumab as needed. The trial did not meet its primary endpoint goal of decreasing the frequency of ranibizumab injections and did not show a significant difference in BCVA in those who completed the trial. However, subgroup analysis showed that in patients with occult CNV < 10 mm² in size, there was a marked VA benefit of combination therapy, as the combination group gained 5.3 more letters than the ranibizumab monotherapy group (11 letters vs. 6 letters) at 36 weeks [60]. Given the recent study readouts from other anti-VEGF/PDGF combination therapy agents, Ohr Pharmaceutical announced in February 2017 that it was pausing enrollment in its phase 3 trial (NCT02727881). The pause was not related to any safety issue, and the more than 200 patients currently enrolled in the study still continue to receive therapy. Further analysis will be based on the existing subject cohorts [61].

7.4.4. Regorafenib

Regorafenib (Bayer Healthcare) is a multi-kinase inhibitor that acts on intracellular signaling of VEGF-A and PDGF receptors. It was developed as a topical eyedrop given three times daily to treat nAMD. The Phase 2a DREAM study (NCT02222207) did not show efficacy that was comparable to previously existing nAMD treatments, and all 21 enrolled patients required rescue ranibizumab treatments. Studies on regorafenib have been halted [62].

7.4.5. LHA510

Alcon has developed a topical anti-VEGF-A medication, LHA510, that has been tested as maintenance therapy for patients with nAMD. The phase 2 study (NCT02355028) compares initial ranibizumab plus topical LHA510 for 84 days versus initial ranibizumab plus placebo, with the primary endpoint being number of patients requiring rescue ranibizumab injections before day 84 [63].

7.5. Sustained delivery treatments

7.5.1. Ranibizumab port delivery system

The need for frequent intravitreal injections has spurred several companies to develop sustained-release anti-VEGF-A devices. The ranibizumab Port Delivery System (PDS), which is a nonbiodegradable port fixed to the sclera, has a reservoir that can be refilled in the office. Phase 1 results indicated that it improved VA comparable to monthly ranibizumab injections as reported in the MARINA and ANCHOR studies. The 20 patients in the trial gained a mean of 10 ETDRS letters and had a mean of 4.8 refills given at 12-month follow-up. Three serious adverse events (related to the implantation procedure) were reported, including endophthalmitis and persistent vitreous hemorrhage. In 2015, Genentech initiated a phase 2 study, the LADDER trial (Long Acting Delivery of Ranibizumab, NCT02510794), to test the safety and efficacy of the PDS on a larger scale, with focus on optimizing treatment dose and refill intervals [64].

7.5.2. GB-102

GB-102 (GrayBug Vision) is Sunitinib maleate, a multitargeted TKI with activity against both VEGF-A and PDGF. It is an injectable depot designed for twice per year formulation. The drug is encapsulated within bioerodible polymer nanoparticles that slowly degrade over time. The patented GrayBug formulation is designed to avoid the inflammatory response seen with other nanoparticles, and the nanoparticles remain at the injection site to avoid clouding the visual axis. In a rabbit laser CNV model, GB-102 showed promising results compared to aflibercept, according to data published on the GrayBug website. Aflibercept is maximally effective when given at the same time as the laser injury, whereas GB-102 demonstrated equal efficacy when given 10 weeks prior to the laser injury. Phase 1 studies are in development [65].

7.5.3. NT-503 encapsulated cell therapy (ECT) implant

NT-503 (Neurotech) is essentially a reversible gene therapy. ECT is an intravitreal implant inserted through a 3-mm scleral incision, which houses an RPE cell line genetically engineered to produce therapeutically active biologics for at least 2 years. NT-503 is a novel VEGF-A receptor fusion protein that is continuously secreted by the platform. Interim results of a phase 2 pilot study indicated that NT-503 ECT was safe and well-tolerated. A dose-response was observed, with meaningful reduction in macular thickening and improvement in vision seen in the subjects who had exposure to two initial ECT implants [66]. More recently, however, a Neurotech press release announced that the phase 2 study (NCT02228304) was discontinued due to a larger than expected number of participants requiring rescue medication in the treatment arm [67].

7.5.4. Hydrogel anti-VEGF depot

Ocular Therapeutix has developed a hydrogel depot that uses polyethylene glycol to create a sustained drug delivery system for anti-VEGF-A that can last for 6 months. The hydrogel creates a tight meshwork that contains the anti-VEGF-A

particles and gradually dissolves, allowing the medication to diffuse. The released anti-VEGF-A particles have been stable and have not demonstrated chemical changes. Phase 1 studies of the hydrogel depot are on the horizon [68].

7.5.5. Durasert

Durasert (pSivida corp) is a bioerodible implant system. Using this technology, PSivida is developing a sustained release system for TKIs that inhibit both VEGF-A and PDGF. IND-enabling studies with this treatment implant are underway [69].

7.5.6. ENV1305

ENV1305 (Envisia Therapeutics) is a sustained release anti-VEGF-A that utilizes PRINT® nanoparticle technology, which according to the company website is a proprietary system capable of engineering highly precise nanoparticle systems, with potential for better control of drug release. Envisia hopes to develop biodegradable PRINT particle implants that can be placed in specific compartments of the eye to optimize therapeutic index and dosing. Preclinical studies began in 2016 [70].

7.6. Gene therapy

Recently, the eye has become a target for investigational gene therapy due to monogenic nature of many inherited retinal diseases, its accessibility, tight blood-ocular barrier, the ability to noninvasively monitor for functional and anatomic outcomes, as well as its relative immune privileged state. Gene therapy for nAMD offers promise of long-term continuous expression of therapeutic anti-angiogenic proteins with a single administration. Viral vectors are conduits for transferring desired genetic information to host cells. Vectors currently used in ocular gene therapy clinical trials include adeno-associated virus (AAV), small single-stranded DNA viruses of the parvovirus family, and lentivirus, RNA viruses of the retrovirus family. Both can transduce non-dividing cells, but AAV are non-integrating, while lentivirus integrate their genome into the host cell genome, and have larger transgene capacity (approximately 10 kb vs. 4.5–5.0 kb for AAV). After successful transduction, the target cells transcribe and translate the viral genetic material into therapeutic protein, which then modulates the pathogenesis of the targeted disease process.

7.6.1. rAAV.sFLT-1 (AVA-101)

The first candidate to emerge from Adverum's (formerly known as Avalanche Biotechnology's) Ocular Biofactory™ platform, rAAV.sFLT-1 (also called AVA-101) uses AAVs, which are not pathogenic in humans. One subretinal injection of rAAV.sFLT-1 creates an Ocular Biofactory, which secretes the natural anti-VEGF-A inhibitor, soluble fms-like tyrosine kinase-1 (sFLT-1). As a potential one-time treatment, the goal of this gene therapy was to reduce the treatment burden associated with current repeated anti-VEGF injections. .

The phase 1 study (NCT01494805) results were published in 2015, with 3-year outcomes published in 2017 [71,72]. Their techniques included performing pars plana vitrectomy (PPV)

followed by the subretinal injection of a low-dose (1×10^{10} vector genomes (vg)) or high-dose (1×10^{11} vg) vector at a location adjacent to the vascular arcades, superior and temporal to the fovea and contiguous with disease-associated subretinal fluid. All patients received ranibizumab injections at baseline and week 4, and as needed thereafter according to prespecified criteria for active nAMD based on ETDRS BCVA, optical coherence tomography (OCT), and fluorescein angiography (FA) findings. At 3 years follow-up, there were no safety concerns beyond those expected from the procedure itself, and patients with the higher dose of viral vector required fewer intravitreal anti-VEGF injections than the low dose and control groups [72].

In the phase 2a randomized clinical trial, patients were randomized to either subretinal rAAV.sFLT-1 gene therapy ($n = 21$) or to the control group ($n = 11$). Patients in the gene therapy group received subretinal rAAV.sFLT-1 (1×10^{11} vg) following PPV. All patients received ranibizumab injections at baseline, week 4, and as needed thereafter following the prespecified criteria for subretinal fluid indicative of active nAMD; ophthalmic and systemic endpoints were assessed at 12 months. Similar to the phase 1 results, there were no systemic side effects and no serious ocular adverse events associated with rAAV.sFLT-1 administration. Three of the patients treated with rAAV seroconverted following injections, suggesting a systemic immune response to the viral particles, but patients did not experience any associated ocular inflammatory response or related systemic symptoms. As would be anticipated following PPV, 11 patients developed a cataract in the therapeutic arm [73].

In the rAAV.sFLT-1 group, BCVA improved by a median of 1.0 letter from baseline compared to a median of -5.0 letters change in the control group. This loss in the control group was largely related to 3 of 11 patients who lost in excess of 20 letters caused by complications of the natural history of nAMD [73]. When these three patients were removed from the analysis, there was no statistically significant difference in BCVA improvement between the gene therapy and the control groups. The median number of ranibizumab retreatments was 2.0 for the gene therapy group compared to 4.0 for the control group [73]. The retina and investment communities viewed the trial results as a disappointment, as both the control and treatment groups meaningfully underperformed compared to the 7.2 and 11.3 ETDRS letter improvement in the landmark MARINA and ANCHOR trials, respectively [4,13].

7.6.2. ADVM-022/ADVM-032

Following the disappointing results from this phase 2a trial, Avalanche Biotechnologies merged with Annapurna Therapeutics to become Adverum Biotechnologies [74]. Their next-generation gene therapy products for AMD, ADVM-022 and ADVM-032, utilize an AAV vector that has been optimized for intravitreal injection of vectors carrying anti-VEGF cDNA, leading to the expression of aflibercept and ranibizumab, respectively. These therapies are in the preclinical research phase [75]. According to publicly disclosed corporate materials, both ADVM-022 and ADVM-032 inhibit laser-induced CNV in a primate model at day 28, comparable in extent to intravitreal injections of aflibercept and ranibizumab, respectively. ADVM-022 has been

selected to advance, with ongoing preclinical studies to assess for anti-VEGF protein expression beyond 20 weeks [76].

7.6.3. AAV2-sFLT01

Sanofi Genzyme investigated intravitreal delivery of AAV2-sFLT01 (NCT01024998). The sFLT1 produced by this company is similar to that used in the Avalanche studies, except that it is a fusion protein of the sFLT-1 domain 2 with the Fc domain of IgG1. In a phase 1, dose-escalation trial, 19 patients with advanced nAMD were treated with a single 100 μ L intravitreal injection of AAV2-sFLT01 according to four dose-ranging cohorts (cohort 1: 2×10^8 vg; cohort 2: 2×10^9 vg; cohort 3: 6×10^9 vg; and cohort 4: 2×10^{10} vg, $n = 3$ per cohort) and one maximum tolerated dose cohort (cohort 5: 2×10^{10} vg, $n = 7$). The results of this trial were recently published in May 2017 [77]. Two patients who received 2×10^{10} vg experienced adverse events deemed to be related to the study drug. One patient had pyrexia that resolved within 3 h. The second patient developed intraocular inflammation 1 month after injection and was successfully treated over 5 weeks with a topical steroid. There was no reported systemic detection of the AAV2-sFLT01 vector or immunogenicity to the vector.

None of the patients in cohorts 1–3 had detectable concentrations of sFLT01 in aqueous humor (AH), but 5 of 10 patients in cohorts 4 and 5 had concentrations of sFLT01 above the limit of quantification at one or more times during the study period, suggesting a dose-related effect. At week 52, four of 19 patients (2 from cohorts 1–3 and 2 from cohorts 4/5) showed sustained reductions of central subfield thickness on OCT suggesting sustained vector related anti-permeability. BCVA assessments were difficult to assess in this study due to the variability in baseline fluid and retinal scarring among the participants of each cohort [77]. The company has not expressed any plans to continue development of this therapy.

7.6.4. RGX-314

Regenxbio is developing a novel AAV8 vector, RGX-314, which expresses a soluble anti-VEGF monoclonal antibody fragment in transduced retinal cells. The company suggests that their proprietary gene delivery platform (NAV® Technology Platform) may yield higher levels of anti-VEGF expression than earlier generation AAV vectors. RGX-314 is to be delivered via subretinal injection during vitrectomy and a phase 1, open-label dose escalation trial (NCT03066258) is scheduled to commence in 2017. Three doses will be assessed in 18 subjects with previously treated nAMD. The primary endpoint involves safety assessments at 26 weeks. Secondary endpoints, assessed at 106 weeks, include change in BCVA, change in central retinal thickness, mean number of rescue anti-VEGF injections, mean change in area of CNV, and leakage [78].

7.6.5. Retinostat

Retinostat (Oxford Biomedica) is a lentivector platform based on the recombinant equine infectious anemia virus. It is delivered by subretinal injection and encodes the antiangiogenic proteins endostatin and angiostatin [79]. A bicistronic expression cassette leads to production of both molecules from one lentivirus vector. This approach derives from preclinical work demonstrating that direct intravitreal injections of either AAV-endostatin, AAV-

angiostatin, or lentiviral vector-angiostatin significantly inhibited a neonatal murine model of proliferative retinopathy [80,81]. The phase 1 trial (NCT01301443) enrolled 21 patients with advanced nAMD (poorly responsive to anti-VEGF-A therapy) and included 3 dosing cohorts over a 48-week period. Overall, the subretinal injection was safe and well-tolerated. During the surgery, one patient developed macular hole and two developed retinal tears; all complications were managed intraoperatively without sequelae. There were no adverse effects related to the lentivector platform. There were sustained high levels of angiostatin and endostatin expressed in the eye throughout the study, as determined by direct sampling from the anterior chamber. A reduction in leakage on FA occurred in 71% of patients; although only one patient showed a significant reduction in intraretinal/subretinal fluid compared to baseline [82], eyes with end-stage disease were enrolled in this trial, likely limiting any potential benefit.

8. Potential development issues

Anti-VEGF-A therapy has some associated ocular and systemic risks, both real and theoretical. There may be an increase in arteriothrombotic events (stroke and myocardial infarction) associated with intravitreal anti-VEGF-A injections [83]. Repeated injections may also place patients at higher risk of developing complications such as endophthalmitis, retinal pigment epithelium atrophy and tears, retinal tears, traumatic cataract, and ocular hypertension [83–86]. The high cost of some of the currently available anti-VEGF-A treatment options, along with large volume of patients needing indefinite injections, places a strain on the health-care system. As more medication options become available, cost of treatment will continue to be scrutinized in determining the most appropriate management for patients.

9. Conclusion

The development of intravitreal anti-VEGF-A therapy has revolutionized the treatment of nAMD and has spawned a rapidly growing multi-billion dollar pharmaceutical industry. Landmark trials such as the ANCHOR study demonstrated superiority of intravitreal anti-VEGF-A injections over photodynamic therapy in terms of preserving and recovering VA [13]. The most widely utilized anti-VEGF-A medications include bevacizumab, ranibizumab, and aflibercept, although many new drugs are currently being developed to address the shortcomings of anti-VEGF-A treatment. These shortcomings include the need for repeated injections, which is costly and burdensome to patients and the health-care system, along with inability to completely halt the disease process of nAMD.

Drugs in the pipeline aim to modulate synergistic targets such as the Tie-2 receptor, Ang-2, and PDGF, with hopes of outperforming anti-VEGF-A monotherapy. Other drugs utilize sustained release therapy, nanoparticle technology, and smaller molecular size in order to extend the duration of anti-VEGF-A effect. Topical and systemic anti-VEGF-A/PDGF therapies are also being explored in attempt to minimize the need for frequent injections. Gene therapy with viral vectors holds the potential to result in continuous production of therapeutic anti-angiogenic proteins via the retina's own cellular apparatus.

10. Expert opinion

The management of chronic degenerative diseases such as nAMD can be arduous for both the physician and patient. While intravitreal anti-VEGF-A injections have been monumental in reducing severe vision loss in countless patients, it requires a motivated patient to continue treatment indefinitely. Anti-VEGF-A maintenance therapy poses a treatment burden on patients, families, and the health-care system, and patients need to be counseled that preservation of vision is considered a success just as much as recovery of vision. It is not surprising that 'real-world' outcomes of anti-VEGF-A treatment fall short of those obtained in landmark clinical trials. The 'real-world' poses many barriers to treatment (mentioned earlier in this article), which frequently results in inadequate numbers of injections to optimize visual gains.

Investigators have worked to enhance outcomes for nAMD, to address the treatment ceiling of anti-VEGF-A therapy as well as the treatment burden of long-term maintenance. Many believed that anti-VEGF-A/anti-PDGF combination therapy would be the next major step forward; however, 2016 brought disappointing results in the trials of rinucumab/aflibercept and pegpleranib/ranibizumab. The phase 3 trial of the topical VEGF-A and PDGF inhibitor, squalamine lactate, subsequently suspended enrollment in April 2017, possibly in response to these results, although currently enrolled patients will continue to receive treatment and data from the existing cohort of subjects will be analyzed. The oral VEGF-A and PDGF inhibitor, X-82, has potential to reduce anti-VEGF-A injection burden, although there are concerns about systemic side effects that may limit its use in certain patients, and liver enzymes should be monitored in patients taking this medication.

Nevertheless, there are numerous other therapeutics being developed. Brolucizumab and Abicipar pegol are the two agents furthest along in development. The recently released results of the HAWK and HARRIER phase 3 trials indicated that brolucizumab 6.0 mg dosed every 12 weeks after 3 monthly loading doses was noninferior to aflibercept dosed every 8 weeks. However, the recent Novartis press release provided limited information and did not specifically mention the mean number of brolucizumab and aflibercept injections administered throughout the 48-week study period. The retina community eagerly awaits the presentation of the full results. If brolucizumab becomes the first anti-VEGF-A drug approved for 12-week dosing, that would potentially diminish aflibercept's role in the global anti-VEGF market (in a similar manner to how ranibizumab's role has declined in recent years). Further disruption of this market could occur when Allergan announces the results of its phase 3 study, which hopes to demonstrate that abicipar pegol dosed every 12 weeks is noninferior to aflibercept dosed every 8 weeks. The 10% incidence of ocular inflammation, noted in the phase 2b study is an issue to monitor, although Allergan looks to resolve that issue, after having modified the formulation and purification process for the phase 3 trial.

In the future, the spotlight will likely shift more toward drugs that influence the Tie-2 receptor pathway, including Nesvacumab, RG7716, and ARP-1536. Of these, RG7716 is the furthest along the pipeline, with the phase 2b AVENUE study underway currently. Based on its ability to improve macular

thickness and VA in VEGF-A nonresponders in the phase 1 trial, there will be great interest to see if these positive results can be duplicated in a larger patient population.

Regarding extended release formulations of anti-VEGF-A therapy, the ranibizumab Port Delivery System is the furthest in development, given that the NT-503 ECT phase 2 study was discontinued, and the other mentioned platforms have not begun clinical studies yet. Additionally, ranibizumab is the most studied of the anti-VEGF-A drugs, so the only unknown variables focus on the safety and efficacy of the port delivery system, which is being tested further in the phase 2 LADDER trial. In theory, gene therapy with viral vectors could be the ultimate form of sustained anti-VEGF-A treatment, as the eye could develop its own anti-VEGF-A secretory mechanism that would diminish the need for intravitreal injections. None of the reviewed gene therapy treatments for nAMD are close to FDA approval at this time, but this represents an exciting area of research to monitor in the future.

In summary, the pathogenesis of CNV formation in nAMD is complex and includes a wide variety of factors that could be targeted in future treatments. Given the impressive advancements in the treatment of nAMD over the past two decades, there is reason to be optimistic that we will continue to see new breakthroughs in anti-VEGF-A therapy, which will address the limitations of currently available treatments options.

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