Review

Extended Duration Anti-VEGF Therapy for Chorioretinal Vascular Diseases: Successes, Failures and Challenges

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Review

Extended Duration Anti-VEGF Therapy for Chorioretinal Vascular Diseases: Successes, Failures and Challenges

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Abstract: Pathologic angiogenesis is responsible for much of the vision loss that stems from several chorioretinal vascular diseases including neovascular age-related macular degeneration (nAMD), diabetic retinopathy (DR), and retinal vein occlusion (RVO). Because vascular endothelial growth factor (VEGF) serves as a pivotal angiogenic molecule, it has emerged as the primary target for therapeutic drugs. Current anti-VEGF therapy is dominated by bevacizumab, ranibizumab, and aflibercept, all of which have been available for more than a decade, but new drugs, both biosimilars (Byooviz and Cimerli) and drugs whose primary aim is to decrease treatment burden (brolucizumab, faricimab, and the ranibizumab port delivery system), have been approved. Recent failures (conbercept, abicipar, and KSI-301) emphasize the complexity of drug development and the difficulties faced by innovators. Most therapies under development, including tyrosine kinase inhibitors and gene therapy, include VEGF-A blockade as their primary function and aim to extend durability rather than increase peak efficacy. But even as many new drugs look to extend durability, cost containment with mandated use of biosimilars serves to balance the therapeutic landscape.

Keywords: angiogenesis; age-related macular degeneration; diabetic retinopathy; intravitreal injection; retinal vein occlusion; vascular endothelial growth factor

1. Introduction

Angiogenesis is a complex physiologic process that results in new blood vessel growth. In healthy individuals, angiogenesis enables embryonic growth and development, and maintains and repairs damaged organs. However, when angiogenesis occurs pathologically in response to hypoxia or inflammation, it leads to tissue dysfunction and destruction, and promotes solid tumor growth. Angiogenesis requires the upregulation and coordination of several growth factors including acidic and basic fibroblast growth factors, transforming growth factors α and β, hepatocyte growth factor, tumor necrosis factor α, angiogenin, interleukin-8, and angiopoietins, but the critical molecule is vascular endothelial growth factor (VEGF) [1,2].

Soon after VEGF was discovered (1989), ophthalmologists measured elevated concentrations in eyes with neovascular age-related macular degeneration (nAMD), diabetic retinopathy (DR), and retinal vein occlusions (RVOs). Drug development that aimed to bind free VEGF and prevent its binding to and dimerization of the trans-membrane VEGF receptors, quickly resulted in the first drug approvals in 2004 (pegaptanib, bevacizuamb). Anti-VEGF drug development continued with the goal of improving peak efficacy, but when it became increasingly obvious that superior efficacy over anti-VEGF monotherapy was unlikely to be achieved, the goal of treatment shifted to developing drugs that had extended duration of action. This manuscript will discuss recent, current, and future efforts to extend the durability of anti-VEGF therapy.

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2. Basic VEGF Chemistry

2.1. Discovery of VEGF

VEGF, a 40 kDa dimeric glycoprotein (average weight in plasma), stimulates angiogenesis by promoting the proliferation and migration of vascular endothelial cells. VEGF was first discovered by Senger (1983) but was originally named vascular permeability factor [3]. In 1989, Connolly and colleagues purified vascular permeability factor, identified the existence of numerous isoforms, and sequenced the molecular structure using a technology not available to Senger. Leung et al coined the term VEGF, which launched an intense research and development effort to characterize the molecule and inhibit its actions [4,5].

2.2. VEGF Family

VEGF is actually a group of seven protein families (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor (PlGF)) [7,8] that regulate angiogenesis and lymphangiogeneis. Isoforms of VEGF-A, particularly VEGF-A165, are the primary drivers of ocular angiogenesis, and inhibiting their actions has been the focus of ophthalmic drug development [7,9]. In the human retina, Müller cells, astrocytes, retinal pigment epithelial cells, neurons, and vascular endothelial cells are responsible for producing and secreting VEGF-A [2,10].

2.3. VEGF Expression

VEGF expression results from an imbalance between normoxic and hypoxic conditions. Hypoxia-induced stabilization of hypoxia inducible factor-1 upregulates VEGF synthesis [1,2,12–14]. Expression of VEGF is not limited to hypoxic conditions since several growth factors, including epidermal growth factor, insulin-like growth factor-1, and platelet derived growth factor, are responsible for increased VEGF levels. Inflammatory conditions with cytokines such as interleukin (IL)1-β and IL-6 can also increase VEGF [15].

2.4. VEGF Receptors

VEGF binds to and activates three trans-membrane VEGF receptors - VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3 (Flt4). VEGFRs consist of 7 immunoglobulin-like domains in the extracellular region, a transmembrane domain, and an intracellular tyrosine kinase domain [11,16]. VEGFR-1 and VEGFR-2 control angiogenesis, and VEGFR-3 controls lymphangiogenesis. VEGFR-2 activation appears to be most important regulator of ocular angiogenesis, whereas the contribution of VEGFR-1 is not fully known.

VEGF's involvement in angiogenesis stems from its role as a signaling glycoprotein. VEGF triggers a cascade response resulting in endothelial cell proliferation and migration, remodeling of the extracellular matrix by inducing the expression of degenerative enzymes such as matrix metalloproteinases and tissue plasminogen activator, and increasing the permeability of blood vessels by fenestrating the smaller capillaries and venules of the vascular endothelial system [1,2].

2.5. VEGF in Eyes with Chorioretinal Vascular Diseases

Chorioretinal vascular diseases, such as AMD, DR, and RVO, that are often associated with elevated VEGF levels, have a profound effect on the prevalence of vision loss throughout the world. In developed countries, AMD is the leading cause of irreversible vision loss and blindness in the elderly population [23] and in younger, working-aged populations, DR and RVO are the first and second most common causes of retina-related visual loss, respectively [24–27].

Patients with AMD have increased levels of VEGF-A in the vitreous [23,28] and Zhou et al also found elevated levels of VEGF-D. AMD promotes a proinflammatory environment within the retina with cytokines that in turn stimulate the production of VEGF [23].

DR develops because chronically elevated blood glucose damages retinal vessels resulting in localized ischemia. RVOs result from focal occlusion of a retinal vein, which delays venous transit

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and causes retinal ischemia [24–27]. In both conditions, VEGF levels are elevated and angiogenesis is promoted [29,30], and VEGF levels are higher in eyes with more severe disease [29].

2.6. Anti-VEGF and Laser Photocoagulation

A traditional approach to limiting the expression of VEGF has been laser photocoagulation. Laser photocoagulation is performed on peripheral ischemic areas in eyes with DR and RVO to scar the retina, decrease oxygen consumption, and lower VEGF production. This decreases the angiogenic drive and limits the formation of fibrosis and the occurrence of vitreous hemorrhage with long-term efficacy [31,32].

3. Widely Available Anti-VEGF Drugs (Table 1)

3.1. Bevacizumab

Bevacizumab (Avastin®, Genentech, S. San Francisco, CA/Roche, Basel, SW) is a humanized, monoclonal antibody, originally approved by the US FDA (2004) for the treatment of metastatic colon cancer [36] with subsequent approvals for advanced renal carcinoma, recurrent glioblastoma multiforme, and non-squamous, non-small cell lung cancer. For several reasons, bevacizumab is unlikely to be approved for the treatment of ocular diseases [2,35].

Table 1. The table lists the most important anti-VEGF drugs in use and under development for the treatment of choroidal neovascular diseases. Important characteristics of each drug are included.

	Generic Name	Company	Weight (kDa)	Structure	Mechanism of Action	FDA Approved
Bevacizumab	Avastin	Genentech	149	Antibody	Binds to all isoforms of VEGF-A	No, only for colon cancer in 2004
Ranibizumab	Lucentis	Genentech	48	Antibody Fragment	Binds to all isoforms of VEGF-A	Yes, 2006
Aflibercept	Eylea	Regeneron and Bayer	115	Recombinant Fusion Protein (VEGF Decoy)	Binds strongly to VEGF-A and PlGF, relative to VEGF-B	Yes, AMD in 2011 and DME in 2014
Brolucizumab	Beovu	Novartis	26	Single Chain Antibody Fragment	Binds to all isoforms of VEGF-A	Yes, 2019
Faricimab	Vabysmo	Roche	150	Antibody	Binds to VEGF-A and Angiopoietin 2	Yes, 2022
Port Delivery System	Susvimo	Genentech	N/A	Intraocular Implant	Slow continuous, diffusion of ranibizumab	Yes, 2021
Ranibizumab-eqrn (FYB201)	Cimerli	Coherus BioSciences, Inc.	48	Antibody Fragment	Biosimilar to ranibizumab	Yes, 2022
Ranibizumab-nuna (SB11)	Byooviz	Samsung Bioepis and Biogen	48	Antibody Fragment	Biosimilar to ranibizumab	Yes, 2021
Abicipar Pegol	Abicipar	Allergan	34	Designed Ankyrin Repeat Protein	VEGF-A	No, new formulation in phase 2 trials

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Conbercept	Lumitin	Chengdu Kanghong Biotech Co., Ltd.	143	Recombinant Fusion Protein (VEGF Decoy)	Similar to aflibercept	No, yet to complete phase 3 trials
KSI-301	N/A	Kodiak Sciences	950	Antibody Biopolymer Conjugate	VEGF-A	No, in phase 3 trials
Aflibercept 8 mg	Eylea	Regeneron and Bayer	115	Recombinant Fusion Protein (VEGF Decoy)	----------	Yes, 2023
OPT-302	Opthea	Opthea	140	Recombinant Fusion Protein (VEGF Decoy)	VEGF-C and VEGF-D	No, phase 2 trial completed
GB-102	Sunitinib Maleate	GrayBug Vision	N/A	Tyrosine Kinase Inhibitor	VEGF-A and PDGF	No, in phase 2 trials
RGX-314	N/A	Regenxbio	N/A	AAV8 Genome Vector	Similar to ranibizumab	No, in phase 2/3 trials
ADVM-022	N/A	Adverum Biotechnologies	N/A	AAV2 Genome Vector	Similar to aflibercept	No, in phase 2 trials

Despite the off-label status of bevacizumab, ophthalmologists take advantage of its availability and low-cost to make it the most commonly used intraocular anti-VEGF drug among US physicians [37–40]. Off-label use of bevacizumab depends upon safe compounding of the drug from intravenous vials by national specialty pharmacies. Fractionation of drug significantly lowers the price of therapy with cost of one year of therapy estimated at $2,924.60, compared to $25,759.20 and $13,954.70 for ranibizumab and aflibercept, respectively [41]. Because bevacizumab is comparably effective as the branded drugs for most patients with a similar safety profile, the large price differential explains why it holds a significant share among ocular anti-VEGF drugs in most world markets.

Bevacizumab is a recombinant murine antibody with a molecular weight of 149 kDa. It binds all isoforms of VEGF-A, thereby blocking their interaction with transmembrane receptors, and preventing intraocular angiogenesis [35]. After intravitreal injection, bevacizumab is transported along actin filaments via myosin pathways through the epithelial barrier and into the subretinal space [42]. This uptake process can be adversely affected if RPE cells are damaged since they initiate the first stage in this cascade [42]. Bevacizumab has an intravitreal half-life of 9.8 days and a binding affinity to VEGF-A165 that is weaker than other anti-VEGF drugs, thus limiting its durability and requiring repeated injections to sustain its actions [35].

Soon after FDA approval of bevacizumab, the ophthalmic community began to assess its efficacy in treating retinal disease. Rosenfeld et al assessed the use of 1 mg intravitreal bevacizumab in a patient with macular edema due to CRVO and in another with nAMD. Within a week, visual acuity improved and fluid resolved through the four-week follow-up. The results from these two patients led to widespread use of bevacizumab for the treatment of chorioretinal vascular conditions [43].

Moshfeghi et al studied the efficacy of intravenous bevacizumab in 18 patients with nAMD. The 24-week treatment regimen consisted of baseline infusions of bevacizumab (5 mg/kg) with additional as-needed infusions at 2-week intervals. The mean visual acuity improved by +14 letters and the mean CRT improved by -112 μm. The only adverse effect was a slight elevation of systemic blood pressure, which was controlled by oral antihypertensive medications. Despite the impressive efficacy and acceptable safety profile, the authors concluded that a larger study was not feasible because intravitreal bevacizumab was being developed as a preferred treatment modality [44].

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3.2. Ranibizumab

Ranibizumab (Lucentis®, Genentech, S. San Francisco, CA/Roche, Basel, SW), which was approved by the US FDA in 2006, is a 48 kDa humanized antibody fragment (Fab) [45]. Antibody fragments are thought to penetrate deeper into the retina than full-length antibodies, which may lead to higher tissue concentrations [46]. With the substitution of five amino acids, ranibizumab was affinity enhanced with a 5 to 20 fold increase in binding affinity to VEGF [47].

The ANCHOR and MARINA 2-year registration trials compared monthly ranibizumab with photodynamic therapy and sham, respectively [48,49]. Patients with predominantly classic CNV in ANCHOR improved by a mean of +11.3 letters with 0.5 mg ranibizumab compared to -9.5 letters in those in the sham cohort. Two of 140 patients in the 0.5 mg group developed endophthalmitis and one had a serious uveitis. In MARINA subjects receiving 0.5 mg ranibizumab improved by +7.2 letters compared to -10.4 letters in the sham group. Endophthalmitis developed in five subjects receiving ranibizumab with serious uveitis seen in six.

Stephian et al examined patients who were switched from bevacizumab ranibizumab and found no changes in either visual acuity or injection frequency [50].

To better determine the relative efficacies and safeties of bevacizumab and ranibizumab, several national trials were conducted. The Comparisons of Age-Related Macular Degeneration Treatments Trials (CATT) [51] randomized 1208 subjects to receive 0.5 mg ranibizumab or 1.25 mg bevacizumab monthly or as needed. Mean visual acuity improvements were similar for patients treated monthly (+8.5 (ranibizumab) and +8.0 letters (bevacizumab)) or as needed (+6.8 (ranibizumab) and +5.9 (bevacizumab)), though patients receiving ranibizumab had a greater mean decrease in CRT (-196 μm) and a higher likelihood of having a dry macula. Subjects receiving as needed therapy required fewer ranibizumab (6.7) injections than bevacizumab (7.6). Patients receiving bevacizumab had a higher rate of systemic adverse events (24.1% vs 19%), but rates of death, myocardial infarction, or stroke was similar between the groups.

The Inhibition of VEGF in Age-related choroidal Neovascularization (IVAN) trial (ISRCTN92166560) was conducted with similar study parameters as those of CATT - 0.5 mg ranibizumab and 1.25 mg bevacizumab were administered monthly or as needed (PRN) with monthly evaluations [52]. Whereas patients in CATT received single injections for recurrences, those in IVAN trial received three monthly injections before being observed. Visual acuity improvements were similar between the two drugs with only a +1.37 letter difference (in favor of ranibizumab). Serious adverse events were also comparable but patients in the discontinuous (PRN) groups had higher mortality rates.

The French national trial (GEFAL; NCT01170767), the Netherlands national trial (BRAMD), and the Austrian national trial (MANTA) also showed comparable changes in BCVA between patients treated with bevacizumab and ranibizumab [53,54]. Adverse event rates were comparable between the two drugs.

The Norwegian national trial (LUCAS; NCT01127360) evaluated the treat and extend regimen. By the end of year two, the changes in BCVA and CST were comparable to those at the end of year one and were similar between the two drugs. Importantly, bevacizumab and ranibizumab groups received a similar number of injections (8.9 vs. 8.0) at the end of year one, but by the end of year two, the difference was significant (18.2 vs. 16.0, respectively). The bevacizumab group had fewer atherothrombotic (1.4%) and cardiac (4.5%) events compared to that of ranibizumab.

The national studies demonstrated that bevacizumab and ranibizumab had comparable peak efficacies though ranibizumab had a better effect on CRT. The PRN trials hinted that ranibizumab has a longer duration of action and this was subsequently verified by the LUCAS trial. A retrospective analysis of treatment patterns following the CATT findings showed that ophthalmologists who favored ranibizumab beforehand more often switched to bevacizumab, and those who favored bevacizumab continued to favor it afterwards [56].

Initial drug development focused on increasing the maximum change in BCVA, but by 2012 it became clear that improvements with anti-VEGF therapy may have hit a “ceiling,” which pushed investigators to pursue durability. Individualized therapy with PRN regimens required fewer

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injections than with fixed dosing regimens but still required regular (monthly) office visits [38,58]. The LUCAS trial showed that treat and extend regimens produced BCVA changes comparable to fixed dosing while requiring fewer injections and fewer clinic visits. Treat and extend quickly became the preferred regimen of most US retina specialists. Fortunately, once the maximum treatment interval is determined, injections at each visit effectively prevent disease re-activation [57].

Proactive treatment regimens (monthly or treat and extend) produce better outcomes than PRN because disease re-activation is allowed to occur at most once [38,58]. In a one-year study by Li et al, the mean number of injections was 12 for the monthly, 9.6 for treat and extend, and 7.4 for the PRN group [58]. In other studies, treat and extend groups had improvements in BCVA that were non-inferior to monthly groups [59–62]. Treat and extend therapy has become an effective economic alternative, since BCVA changes are non-inferior to those from monthly regimens, and time and money is saved because fewer clinic visits are required [46].

3.3. Aflibercept

Aflibercept (Eylea®, Regeneron, Tarrytown, NY) is a recombinant fusion protein containing the 2nd extracellular binding domain of VEGFR-1 and the 3rd domain of VEGFR-2 combined with the Fc portion of a human IgG1. This 115 kDa dimeric glycoprotein functions as a soluble VEGF decoy receptor that binds strongly to isoforms of VEGF-A and PlGF, and weakly to VEGF-B. Aflibercept was approved by the FDA for neovascular AMD (2011), DME (2014), and subsequently for DR, RVOs, myopic CNV, and retinopathy of prematurity [63,64]. Because of aflibercept's high binding affinity (0.5 pM for VEGF165) and long intravitreal half-life (11 days), developers hoped to demonstrate longer durability.

The randomized, double-masked, phase 3 VIEW 1 (NCT00509795) and VIEW 2 (NCT00637377) trials evaluated 2,457 patients with nAMD [65,66]. Patients were randomized into four treatment cohorts: monthly 0.5mg ranibizumab, monthly 2 mg aflibercept, monthly 0.5 mg aflibercept, and 2 mg aflibercept every 8 weeks following 3 monthly loading doses. After 52 weeks, the regimens were changed to PRN dosing with a 12-week cap. The average gains in BCVA were similar among cohorts, with patients improving by +8.3 to +9.3 letters by week 52, and +6.6 to +7.9 letters by week 96. Through week 96, the numbers of injections were 16.5 for monthly 0.5 mg ranibizumab, 16 for monthly 2 mg aflibercept, 16.2 for monthly 0.5 mg aflibercept, and 11.2 for the 8-week 2 mg aflibercept group. Arterial thromboembolic events were similar across the cohorts (2.4% to 3.8%)

As with ranibizumab, aflibercept has been studied with the treat and extend protocol. In both clinical studies and meta-analyses, treat and extend groups were non-inferior to both monthly and bi-monthly fixed regimens [38,67]. Compared to ranibizumab treat and extend groups, aflibercept treat and extend produces comparable changes in BCVA with similar numbers of injections [68].

3.4. Brolucizumab

Brolucizumab (Beovu®, Alcon, Geneva, SW) is a 26 kDa single chain antibody fragment that inhibits all isoforms of VEGF-A [38]. Animal studies have demonstrated that the small molecular size enables better retinal penetration and faster clearance [69]. The 6 mg dose of brolucizumab is more than 10 times the molar dose of aflibercept, and about 20 times that of bevacizumab and ranibizumab [69]. The high molar dose partly makes up for the short intravitreal half-life by allowing some patients to be treated at 12-week intervals. Brolucizumab was approved by the FDA in 2019 for the treatment of AMD and in 2022 for DME [70].

The phase 3 HAWK (NCT02307682) and HARRIER (NCT02434328) trials investigated brolucizumab in treatment naïve patients with nAMD [71,72]. These double-masked, multicenter, active-controlled trials, randomized 1,817 patients to receive 3 mg brolucizumab (HARRIER only), 6 mg brolucizumab, or 2 mg aflibercept. In both trials, three monthly loading doses were administered and brolucizumab groups were extended to q8wk or q12wk depending on disease activity. Injection intervals were reduced to q8wk if visual acuity dropped; aflibercept groups were injected q8wk. At the 48-week primary endpoint, brolucizumab was non-inferior to aflibercept regarding changes in BCVA (HAWK: +6.1 letters for 3 mg brolucizumab, +6.6 letters for 6 mg brolucizumab, and +6.8 for 2

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mg aflibercept; HARRIER: +6.9 for 6 mg brolucizumab and +7.6 for 2 mg aflibercept). The 6 mg brolucizumab groups showed less disease activity than aflibercept at the 16-week checkpoint (HAWK: 24% vs 34.5%, HARRIER: 22.7% vs 32.2%) and produced greater CST reductions (HAWK: -172.8 μm vs -143.7 μm; HARRIER: -193.8 μm vs -143.9 μm). Overall, adverse events were similar among cohorts.

By the end of two years, significant numbers of brolucizumab-treated patients had disease recurrence requiring interval reduction to q8wk. Fewer than 50% of patients receiving brolucizumab were maintained on q12wk dosing.

After approval, increased incidences of intraocular inflammation, retinal vasculitis, and occlusive vasculitis were noted in brolucizumab-treated patients [73]. In February, 2020, the American Society of Retinal Specialists (ASRS) reported that they had received 14 cases of brolucizumab related vasculitis, 11 of which were considered occlusive. Baumal et al reported that the intraocular inflammation after intravitreal injection of brolucizumab can range from peripheral vasculitis to occlusion of large retinal arteries with severe vision loss [74]. The reports of occlusive vasculitis combined with the disappointing number of patients maintained on q12wk therapy have limited the use of brolucizumab in the US.

3.5. Faricimab

Faricimab (Vabysmo®, Genentech, S. San Francisco, CA/Roche, Basel, SW) is a 150 kDa bispecific antibody that binds both VEGF-A isomers and angiopoietin 2 [75,76]. Angiopoietin 2 binds to the Tie 2 receptor to limit vascular permeability, vascular endothelial cell proliferation, and inflammation [77]. With this dual mechanism of action, the developers hoped that faricimab might further limit angiogenesis by providing additional stability of the vascular endothelial cells [75,77]. Faricimab was approved by the US FDA for treatment of nAMD and DME in 2022 [76].

The multi-center, phase 3 registration trials TENAYA (NCT03823287) and LUCERNE (NCT03823300) randomized 1,329 patients with untreated nAMD to 2 mg aflibercept q8wk after 3 monthly loading doses or 6 mg faricimab q8wk (or up to q16wk according to a personalized treatment interval based on qualifying evaluations at weeks 20 and 24) [78,79]. Both trials showed non-inferiority of faricimab to aflibercept (TENAYA: aflibercept +5.1 letters, faricimab +5.8 letters; LUCERNE: aflibercept +6.6 letters, faricimab +6.6 letters), with similar incidences in ocular adverse effects (aflibercept 36.2% to 38.1% vs. faricimab 36.3% to 40.2%). Faricimab was concurrently evaluated for DME in the YOSEMITE and RHINE trials and was shown to be non-inferior to aflibercept.

3.6. Biosimilars

Biosimilars are protein macromolecules, similar to their originator drugs that are created through reverse engineering. Once synthesized, biosimilars are produced within living cell assays [80]. Biosimilars require a shorter time line for development with fewer trials and patients, and a much lower financial commitment from the manufacturer [81]. Biosimilars can be introduced to the market once the originator drug comes off patent.

Biosimilars are predicted to produce similar clinical results to the originator drug but at a lower cost. Mulcahy et al estimated that biosimilars could save $54 billion in direct consumer spending by 2026 [82]. Lucentis has been used extensively since its introduction in 2006, but since it has now come off patent, biosimilars such as Cimerli and Byooviz have been introduced to the market [38–40,83].

Cimerli (FYB201, ranibizumab-eqrn) is a ranibizumab biosimilar available in 0.5 mg and 0.3 mg doses [84]. In the phase 3 of the COLUMBUS-AMD trial (NCT02611778), 0.5 mg Cimerli was tested against 0.5 mg ranibizumab in 477 patients with treatment-naïve nAMD [85]. Cimerli was found to be comparable to ranibizumab both in terms of visual acuity (+7.8 letters vs. +7.9 letters) as well as the rate of adverse events (both groups at 8.4%) [84] Since Cimerli is available in both doses, it has been approved for the same indications as ranibizumab: nAMD, RVO, DME, DR, and mCNV [86]. The wholesale price of Cimerli is approximately 30% below that of ranibizumab [83].

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Byooviz (SB11, ranibizumab-nuna) was evaluated in the phase 3, double-masked, parallel-group trial (NCT03150589) in which 705 patients with nAMD were randomized to receive monthly intravitreal injections of 0.5 mg Byooviz or ranibizumab over the course of 52 weeks [87,88]. By the end of the study, Byooviz produced similar changes in BCVA (+9.8 vs. +10.4 letters), central retinal thickness (-140 μm vs -125.1 μm), and ocular adverse events (32% vs 29.7%). Because Byooviz is only available as a 0.5 mg dose, it is indicated for nAMD, RVO, and mCNV, but not diabetic retinopathy [89]. Byooviz is 40% less costly than ranibizumab, was approved by the US FDA in late 2021, and became commercially available in 2022 [81].

More ranibizumab biosimilars are in development and aflibercept biosimilars are expected to be available in 2025 when Eylea patents expire. Biosimilars are expected to produce similar clinical responses as their originator drugs at a lower price, but improved durability is not expected.

3.7. Ranibizumab Port Delivery System

Anti-VEGF treatment has been based on repetitive intravitreal injections at intervals that range from 4 to 16 weeks. The need for frequent injections and monitoring along with numerous clinic visits can burden physicians' offices and strain patient compliance [90]. Neurotech's encapsulated cell technology uses immortalized retinal pigment epithelial cells implanted into the vitreous to overproduce a drug. Phase 3 testing with ciliary neurotrophic factor is ongoing for patients with macular telangiectasia but previous trials for geographic atrophy, retinitis pigmentosa, and nAMD failed.

The ranibizumab port delivery system (PDS, Susvimo®, Genentech, S. San Francisco, CA/Roche, Basel, SW) is a surgically planted sustained release reservoir that elutes ranibizumab into the vitreous [90]. The reservoir is periodically filled with highly concentrated ranibizumab that passively diffuses down a concentration gradient through a porous titanium release membrane [91]. The port delivery system was approved by the US FDA in 2021 and is indicated for adults with nAMD that have positively responded to at least 2 prior anti-VEGF intravitreal injections.

The phase 2 LADDER (NCT02510794) trial compared the PDS filled with different concentrations of ranibizumab (10 mg/ml, 40 mg/ml, and 100 mg/ml) against monthly injections of 0.5 mg ranibizumab [92]. The phase 3 ARCHWAY (NCT03677934) trial compared q6month refills of the PDS with monthly injections of ranibizumab in 418 patients with nAMD [93]. At the 96-week mark, patients treated with the PDS had similar changes in BCVA and CST compared with 0.5 mg ranibizumab. Overall, the results demonstrated that the port delivery system was noninferior to the monthly control.

The safety profile of the PDS has raised some concerns among surgeons. Ocular adverse events were more common in patients with the PDS (19% vs. 6%) and the rate of endophthalmitis (1.6%) prompted the FDA to place a "black box" warning on the package insert. Conjunctival coverage of the implant remains a problem to which surgeons must be vigilant.

In October of 2022, Genentech voluntarily withdrew the PDS from the market because of septal dislodgement [94]. The company is redesigning the septum and is hoping to reintroduce the PDS in late 2024 [95].

4. Anti-VEGF Drug Failures

4.1. Abicipar

Abicipar-pegol is a small, designed ankyrin repeat protein (DARPin) [96] with high affinity for VEGF-A [97]. The low MW limits the intravitreal half-life, so the developers added a pegol moiety to extend its durability. The 52-week phase 3 CEDAR (NCT02462928) and SEQUOIA (NCT02462486) trials randomized 1,888 patients with treatment naïve nAMD into 3 cohorts: 2 mg abicipar every 8 weeks after 3 monthly loading doses, 2 mg abicipar every 12 weeks after 3 monthly loading doses, and a control of monthly 0.5 mg ranibizumab [98,99]. Abicipar was noninferior to ranibizumab in terms of BCVA (+7.5 letters, +6.4 letters, and +8.4 letters) and CRT changes (-144 μm, -145 μm, and -144 μm) but had significantly more associated ocular adverse events. Patients receiving q8wk and

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q12wk abicipar had high incidences of inflammation (15.4% and 15.3%) compared to the control group (0.3%) though new inflammatory events in the second year of the trial were considerably less frequent (+0.8%, 2.3%, and 1.0% respectively). Due to these high rates of intraocular inflammation, the FDA denied approval for abicipar. The inflammation has been attributed to manufacturing in bacterial systems [97,100] and a modified process in the phase 2 MAPLE trial (NCT01397409) decreased the inflammation but not enough to continue development [100,101].

4.2. Conbercept

Conbercept (KH902) is a recombinant fusion protein with human protein sequences that serves as a VEGF decoy receptor. This 143 kDa protein contains the 2nd extracelluar Ig binding domain of VEGFR-1 and the 3rd and 4th domains of VEGFR-2 fused to the Fc portion of human IgG1 [31]. Conbercept has the capacity to bind to all VEGFA isoforms as well as PlGF [102]. In China, the phase 3 PHOENIX (NCT01436864) trial randomized 114 patients into 2 groups: 3 monthly conbercept injections followed by an injection every 3 months until the 12th month, and 3 monthly sham injects followed by 3 monthly conbercept injections, ending with a conbercept injection every 3 months until the month 12. At the one-year primary endpoint, BCVA improved by +9.98 letters and +8.81 letters in each cohort [103]. The phase 3 PANDA-1 (NCT03577899) and PANDA-2 (NCT03630952) trials were international large-cohort trials that compared conbercept to aflibercept [104,105]. Both trials were terminated in April 2021, removing conbercept from consideration of US FDA approval [106].

5. Extended Durability Drugs in Development

5.1. KSI-301

KSI-301 uses a novel approach to VEGF inhibition by acting as an antibody biopolymer conjugate. The IgG1 VEGF antibody portion is attached to a large biopolymer to increase molecular size to 950 kDa and prolong intravitreal residence time [107,108]. The estimated half-life for KSI-301 in rabbit models is 10.5-12.5 days. These models demonstrated that KSI-301 binds to VEGF-A with a higher affinity then VEGFR-1 and VEGFR-2, making it a powerful inhibitor of angiogenesis [108,109].

The phase 2 DAZZLE (NCT04049266) trial compared 5 mg KSI-301 to 2 mg aflibercept [110]. Patients (559) were randomized at baseline to receive either 3 monthly loading doses of KSI-301 followed by doses every 3, 4, or 5 months, or 3 monthly loading doses of aflibercept followed by doses every 2 doses. KSI-301 was well-tolerated throughout the trial but failed to meet the primary efficacy endpoint of non-inferiority to aflibercept. Patients receiving KSI-301 also had higher rates of intraocular inflammation (3.2% vs. 0%) [111]. Investigators concluded that dosing less frequently than every 12 weeks was insufficient for KSI-301 [112]. Several other trials had been planned - GLEAM (NCT04611152) and GLIMMER (NCT04603937), BEACON (NCT04592419), GLOW (NCT05066230), and DAYLIGHT (NCT04964089) – but further development of KSI-301 is unclear [113–117].

5.2. Aflibercept 8 mg

Aflibercept (Eylea) 8 mg high dose (HD) has been recently developed to extend the duration of action beyond that of aflibercept 2 mg. You et al showed that 4 mg monthly doses were an effective option for refractory and resistant cases of nAMD [118]. This spurred development of 8 mg aflibercept in the phase 3 PULSAR (nAMD, NCT04423718) and PHOTON (DME, NCT04429503) trials [119,120]. Patients in each trial were randomized at baseline to receive aflibercept 2 mg q8wk or aflibercept 8 mg q12wk or q16wk after 3-5 monthly loading doses. Changes in BCVA at 52 weeks were similar between the different cohorts in each trial, and high percentages of patients receiving aflibercept 8 mg were maintained on q12wk or q16wk intervals through 52 weeks. No differences in safety between the 2 mg and 8 mg doses were seen. In August, 2023, the US FDA approved the 8 mg dose for the treatment of nAMD and DME.

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5.3. OPT-302

Whereas VEGF-A acting through VEGFR-2 is considered the major driver of angiogenesis in nAMD, ligands of VEGF-C and VEGF-D may play a supplemental role. Elevated levels of VEGF-C and -D are seen in patients with nAMD and these further increase when intravitreal therapy is used to inhibit VEGF-A [23,73]. OPT-302 (Opthea) is a human recombinant protein with the extracellular binding domains 1-3 of VEGFR-3 bound to the Fc portion of a human IgG1. It serves as a potent inhibitor of VEGF-C and D [73] that may block the auxiliary routes of angiogenesis when used in combination with anti-VEGF-A therapy.

A phase 2b trial assessed the effectiveness of OPT-302 in combination with anti-VEGF-A therapy. Patients (366) with treatment naïve nAMD were randomized to receive monthly ranibizumab 0.5 mg, OPT-302 0.5 mg with ranibizumab, and OPT-302 2.0 mg with ranibizumab. At the 24-week primary endpoint, OPT-302 2 mg/ranibizumab produced greater improvements in BCVA compared to ranibizumab monotherapy (+14.2 letters vs. +10.8 letters) and greater improvements were seen across multiple secondary endpoints. Improvements in BCVA in the OPT-302 0.5 mg/ranibizumab cohort were similar to ranibizumab monotherapy. The phase 3 ShORe and COAST trials will compare OPT-302/anti-VEGF-A against ranibizumab and aflibercept, respectively [121].

5.4. GB-102

GB-102 (sunitinib maleate) is a tyrosine kinase inhibitor with activity against VEGF-A as well as platelet derived growth factor (PDGF) [106,122]. Sunitinib is stored within bioerodible polymer nanoparticles that break down over a six-month period. The nanoparticles not only minimize an inflammatory response but they remain near the injection site, thereby not clouding the patient's visual axis [106]. This extended duration therapy seeks to reduce patient burden by requiring only two injections per year.

In the phase 2 ALTISSIMO trial, 56 patients were randomized to receive GB-102 1 mg at baseline followed by another 1 mg at 6 months, GB-102 2 mg at baseline followed by 1 mg at 6 months, or aflibercept 2 mg x 3 followed by q8wk injections for up to one year. The safety profile of GB-102 was good with no vision threatening inflammation or significant rises in intraocular pressure, but improvements in BCVA for the GB-102 cohorts was less than for aflibercept (-7.4 letters, -5.1 letters, +1.8 letters respectively). Researchers attributed the BCVA changes to "high need patients" and "events of particle dispersion." New formulations of GB-102 are being developed to limit dispersion of the depot under higher stress conditions [123].

5.5. Gene Therapy

Gene therapy is a novel treatment approach for chorioretinal vascular diseases. Exogenous genes that code for an anti-VEGF molecule are introduced into human host cell lines [124] via subretinal (in conjunction with vitrectomy), intravitreal, or suprachoroidal injections. Since the eye is an immune privileged organ, it can accept foreign antigens with decreased risk of subsequent immune responses. The adeno-associated virus (AAV) vector is the choice of delivery systems since it is a non-pathogenic, non-integrating vector that can be easily manipulated, withstands extreme ranges of pH and temperature, and has the capacity to infect a broad range of cells [125,126]. Two leading gene therapies, RGX-314 and ADVM-022, utilizing this vector have emerged.

RGX-314 uses a novel AAV8 vector to deliver a genome that promotes the production of an anti-VEGF antibody fragment, which is similar to ranibizumab [127]. The primary goal of RGX-314 therapy is to improve the patient's quality of life by reducing the number of required intravitreal injections and clinic visits [128]. In a phase 1/2a trial (NCT03066258), 42 patients with severe nAMD were enrolled and randomly divided into 5 cohorts: 3x109 genome copies (GC)/eye, 1x1010 GC/eye, 6x1010GC/eye, 1.6x1110GC/eye, and 2.5x1011GC/eye. All cohorts received ranibizumab injections 2 weeks prior to gene therapy, a 4-week post-treatment injection, and subsequent injections based on monthly evaluations [129]. After the 26-week primary safety endpoint was met, the trial was

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extended to a total of 106 weeks. Mean changes in BCVA for each cohort were as follows: -7.6 letters, +1.2 letters, +14 letters, +0.9 letters, and -3.8 letters respectively. The number of supplemental injections (annualized) were fewer for the higher GC/eye cohorts (10.3, 9.3, 2.8, 4.4, and 2.0 respectively) The extension study showed that 12 of the 42 patients experienced a serious adverse event (usually inflammation), which has led to the recommendation that corticosteroids be used at the beginning of therapy. Planned phase 2 and 3 trials include AAVIATE (NCT04514653), which will test 2 doses of RGX against monthly ranibizumab injections, and ATMOSPHERE (NCT04704921), which will compare 2 doses of RGX against ranibizumab and aflibercept [130,131].

ADVM-022 (Adverum) uses a AAV2 vector that is designed to express an anti-VEGF protein similar to aflibercept [132,133]. In non-primate animal models, therapeutic aflibercept levels have been maintained for up to 30 months [128]. One of the first human nAMD trials, OPTIC (NCT03748784), enrolled several cohorts with increasing doses of the genome [134]. Overall, 15% of the lowest dose cohort needed supplemental aflibercept injections, but only 1% of the highest dose cohort required them. A good safety profile with only minor adverse events was noted. In another early trial, INFINITY (NCT04418427), ADVM-022 was tested on patients with DME [135]. Higher doses of ADVM-022 led to more adverse events, and DME testing was subsequently discontinued.

Other companies, including Genzyme and 4D Molecular Therapeutics, are developing gene therapies using the AAV vector [136].

6. Discussion

6.1. Current Usage Patterns

For years, anti-VEGF use has been dominated by bevacizumab, ranibizumab, and aflibercept. Though off-label for ocular indications, bevacizumab is used throughout the world for treatment of chorioretinal vascular diseases. National studies such as CATT, IVAN, GEFAL, BRAMD, and LUCAS established its safety and efficacy, thereby encouraging physicians, insurers, and government regulatory agencies to use (and sometimes require) bevacizumab as primary therapy. Though bevacizumab has no advantages in efficacy or safety over ranibizumab and aflibercept, price remains the main reason for its popularity. A 2018 study estimated that a year of bevacizumab therapy costs $2,924.60, considerably less than ranibizumab ($25,759.20) and aflibercept ($13,954.70) [41].

An American Society of Retina Specialists (ASRS) survey showed that most US retinal specialists use bevacizumab as first line therapy. According to Medicare spending, aflibercept is the second most frequently used drug (by dollars) and ranibizumab is third. Many US insurers now require “step therapy,” meaning that bevacizumab must be first line therapy, with the “branded” drugs used only if bevacizumab produces an inadequate response.

The introduction of new medications is further changing the drug utilization landscape. Use of brolucizumab since its introduction has been modest, because of concerns over drug-related inflammation. On the other hand, the launch of faricimab has been more successful with steady increases in market share since its introduction. The less expensive ranibizumab biosimilars (Byooviz and Cimerli) have lowered the reimbursements rates of Lucentis and some insurers are requiring the use of a biosimilar rather than Lucentis.

At the time of this writing, aflibercept 8 mg had just been approved, so its impact on drug utilization cannot yet be determined.

6.2. Future Landscape

The future of anti-VEGF therapy will include drugs with extended durations of action, some of which may incorporate novel treatment mechanisms. The future marketplace will likely be shaped by the following three major therapeutic principles: price, efficacy, and patient burden.

The cost of therapy influences some providers’ choice of drugs, and also influences coverage policy by many insurers and national healthcare systems. As populations age and life expectancy increases, cost control will become an increasingly important determinant of drug utilization. Since bevacizumab and the biosimilars lower drug costs, they will play increasingly important roles in the

treatment of patients with chorioretinal vascular diseases. Competition is usually thought to drive consumer drug prices lower, but since physicians and third party payers determine a large share of drug utilization, competition will be limited by factors other than price [82]. Several ranibizumab and aflibercept biosimilars are currently being developed and their entry into the marketplace will expand treatment options and have a controlling effect on overall cost.

Drug efficacy will continue to be considered when physicians and patients choose therapies. Fortunately, anti-VEGF therapy is effective in most patients, but we appear to have reached a therapeutic ceiling with current medications. Until recently, blocking the actions of VEGF-A and PlGF were the only available mechanisms of action, and we think that blocking other biochemical pathways will be needed to incrementally increase efficacy. Improved peak efficacy might be defined as improving vision for the average eye or effectively treating cases of refractory disease.

Because faricimab targets both VEGF-A and ang 2, improved peak efficacy had been hoped for, but neither phase 2 nor phase 3 trials showed superiority over anti-VEGF monotherapy. Some investigators have suggested that ang 2 is a context molecule, meaning that direct ang 2 binding adds very little to effective anti-VEGF monotherapy.

OPT-302 inhibits both VEGF-C and VEGF-D, and is being investigated in combination with anti-VEGF-A therapy versus anti-VEGF-A monotherapy [73]. Dual drug therapy requires a superiority study, which is a very high standard to meet, and phase 3 trials are currently underway. Thus far, no superiority result has been found with any drug and it remains to be seen if OPT-302 can meet this primary endpoint.

Tyrosine kinase inhibitors that block several biochemical pathways are in development. Though increased efficacy had been hoped for with these drugs, recent studies suggest that will not be the case. Instead, the drugs are being developed with extended release formulations to improve durability.

When treated with the anti-VEGF therapies discussed herein, patients undergo frequent intravitreal injections and clinic visits. To minimize the number of visits and improving patient compliance, most physicians have adopted the treat and extend strategy [55]. Regardless of how future drugs are approved for treatment, it's likely that physicians will use some version of treat and extend to minimize burden on the patient and ophthalmic practice while not compromising outcomes.

Gene therapy is being developed as the ultimate extended duration strategy. Successful implantation of genomes has been achieved in early trials with both RGX-314 and ADVM-022 but non-inferior vision results and a good safety profile remain elusive goals. Trials will continue but the long-term outlook for anti-VEGF gene therapy remains uncertain.

Because each anti-VEGF drug has its inherent weaknesses, no ideal therapy has thus far emerged. Therefore, individualized therapy regarding drug and regimen will continue to be favored by most physicians. What we can be sure of through the next decade is that physicians and patients will have more therapeutic options.

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