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REVIEW ARTICLE

# Anti-VEGF and Other Novel Therapies for Neovascular Age-Related Macular Degeneration: An Update

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## Abstract

Age-related macular degeneration (AMD) is a leading cause of visual impairment and blindness in older adults. The prognosis for the neovascular type of advanced AMD improved with the introduction of biological drugs with antiangiogenic properties, beginning with off-label bevacizumab, which was first used intravitreally in 2006. These drugs target newly formed vessels that grow beneath the center of the retina, causing loss of central vision, and they can help to maintain or improve vision. Repeated intravitreal injections are needed to achieve prolonged inhibition of proangiogenic cytokines, primarily vascular endothelial growth factor (VEGF). Major regulatory agencies have approved several molecules for AMD treatment, including ranibizumab, aflibercept, and brolucizumab. The development of further drugs was mainly targeted at prolonging anti-VEGF inhibition—thus reducing the frequency of injections—and expanding the biological targets of proangiogenic cytokine inhibition. Finally, biosimilars are already being marketed in some countries, allowing the containment of costs of AMD treatment, which are growing steadily in many settings because of the need for long-term treatment. This review summarizes the properties and clinical profiles of anti-VEGF biological drugs that are approved to treat neovascular AMD as well as ongoing research on molecules that may be marketed in the near future.

## Key Points

Age-related macular degeneration (AMD) is one of the most common causes of vision loss in older adults. The prognosis of the neovascular form of advanced AMD has improved since the introduction of biological drugs with antiangiogenic properties.

Several molecules that aim to bind vascular endothelial growth factor (VEGF) have been approved for AMD treatment, including ranibizumab, aflibercept, and brolucizumab.

Newer drugs are mainly targeted at prolonging anti-VEGF inhibition to reduce the frequency of injections and at expanding the biological targets of proangiogenic cytokine inhibition.

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## 1 Etiology, Pathogenesis, Epidemiology, and Clinical Outcomes of Age-Related Macular Degeneration (AMD)

Age-related macular degeneration (AMD) affects the central part of the retina, causing progressive loss of central vision [1, 2]. The early stages of AMD are often asymptomatic, and people can be diagnosed with macular drusen during even routine eye examinations. Drusen are due to the accumulation of lipid material, which accumulates in deposits underneath the retinal pigment epithelium (RPE). In advanced AMD stages, the RPE may atrophy completely, first in small focal areas, then sometimes progressing to widespread, or geographic, atrophy. Late AMD can also be exudative, or "wet," when newly formed blood vessels grow under the RPE and, occasionally, into the subretinal space (neovascular AMD [nAMD]). This neovascular tissue (choroidal neovascularization [CNV]) causes subretinal hemorrhage and intraretinal fluid accumulation, which often results in increased scarring of the retina with disruption of the macular tissues. Retinal damage can cause the development of a blind spot in central vision, which initially affects tasks such as reading and face recognition, and can progress to a level that limits mobility and personal autonomy. Once a patient develops nAMD in one eye, the fellow eye is at high risk of developing the same condition within 5 years, also depending on fundus lesions and age [3].

On a global scale, AMD and diabetic retinopathy are the fourth and fifth causes of blindness after cataract, glaucoma, and refractive error. Population aging and growth saw cases of blindness rise by 50–60% between 1990 and 2020, although their age-adjusted prevalence decreased by about 30%. Clearly, aging is the greatest risk factor for AMD. Recent genetic research focusing on polymorphisms showed that genetic risk profiles in East Asian populations resembled those in Europeans and were predicted to result in a large increase in the incidence of AMD over the coming years as compared with Chinese populations [4, 5].

From a clinical perspective, AMD is classified into stages such as early, intermediate, and late based on color fundus photography. With rapid advances in ophthalmic imaging, including the increasing resolution and software processing achieved with optical coherence tomography (OCT) and OCT angiography, the fundus photographic classification has evolved towards an integrated classification based on multimodal imaging of the chorioretinal structure [6]. A systematic review of systematic reviews showed that visual impairment affects quality of life and that numerous interventions, primarily cataract surgery and intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, have a measurable beneficial impact on quality of life [7].

Over the last decade, the treatment of macular disease has been improved with the advent of anti-VEGF drugs such as pegaptanib, ranibizumab, aflibercept, and bevacizumab used off label. In addition, glucocorticoids were also used as therapy for retinal diseases such as diabetic macular edema or retinal vein occlusion. Dexamethasone or fluocinolone implants have the advantage of the longest surgery-free period (not less than 6 months) because of their formulation.

Pegaptanib was the first anti-VEGF approved in AMD but has been completely replaced with the advent of the other drugs. Moreover, different molecules are still under investigation to improve the results already achieved, including biosimilars and drug-delivery systems, as described in detail in Sects. 2.3 and 3.

When reporting evidence for intravitreal anti-VEGF treatments for ocular disease, an important premise is that drug type and treatment regimen are equally key components of treatment effectiveness. Randomized controlled trials (RCTs) typically standardize the treatment regimen to compare drug efficacy, but some RCTs compared different regimens of the same drug. A systematic review showed that less-than-monthly regimens use fewer injections than monthly regimens but have slightly poorer visual function outcomes [8]. Moreover, as-needed (pro re nata [PRN]) regimens, in which injections are delivered when CNV recurs, may be slightly less effective than treat and extend (T&E) regimens, in which CNV recurrence is managed with progressively larger treatment intervals and injections are delivered regardless of whether new recurrence is observed. Unfortunately, a variable and sometimes large gap exists between clinical practice and RCTs, since patients are often undertreated in many clinical settings and any visual benefit with anti-VEGF injections for AMD may be smaller or not maintained in the long term.

This evidence allows us to make a few statements that support the conduct of this review. First, vision impairment is an expanding global health issue that affects quality of life. Second, preventive strategies and therapeutic interventions exist to maintain or restore quality of life in individuals with vision impairment worldwide. Third, geographic differences exist regarding the leading causes of vision impairment. The complications of the most common retinal vascular diseases—diabetic retinopathy and AMD—are treated with intravitreal antiangiogenic therapy using anti-VEGF drugs, of which several molecules exist or are being developed, including biosimilars and drug-delivery systems. Given the huge public health impact in terms of health benefits and use of human and drug resources, the aim of this review was to summarize the evidence on anti-VEGF drugs for treatment of AMD, including their strengths and limitations.

## 2 Anti-Vascular Endothelial Growth Factor (VEGF) Drugs

### 2.1 Approved for Neovascular AMD

#### 2.1.1 Pegaptanib

Pegaptanib sodium was the first anti-VEGF drug approved for intravitreal use in the treatment of nAMD in humans [9, 10]. The molecular structure is an RNA aptamer (polyethylene glycol-linked molecule) that binds the $VEGF_{165}$ and larger isoforms, sequestering $VEGF_{165}$ and therefore preventing it from activating its receptor. Pegaptanib sodium was approved for the treatment of nAMD in 2004 on the strength of the results of the phase III VISION trial [11] (see Table 1 for the full names of trials cited in this review). However, its poorer efficacy compared with other available anti-VEGF drugs means pegaptanib is no longer recommended for treatment and has been completely replaced.

#### 2.1.2 Ranibizumab

**2.1.2.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** Ranibizumab (Lucentis®; Novartis, Basel, Switzerland; Genentech; South San Francisco, CA, USA) is a 48-kDa recombinant humanized immunoglobulin (Ig)-$G1_k$ isotype monoclonal antibody fragment (Fab) devoid of the Fc portion. Ranibizumab binds all VEGF-A isoforms.

The vitreous half-life ($t_{½}$) was 7.2–9 days, and ranibizumab appeared to reach maximum serum concentration approximately 0.5 days after intravitreal administration that was 90,000 times lower than those in the vitreous. The absence of the Fc region makes the molecule susceptible to systemic metabolism, and its serum $t_{½}$ was estimated at 2 h [10].

Previous animal studies reported a vitreous $t_{1/2}$ of 2.88 days after a 0.5 mg/0.05 mL single dose in rabbit, and no serum concentration was detected [12]; studies in two different monkey models reported a vitreous $t_{1/2}$ of 2.63 and 2.73 days, respectively [13, 14] (Table 2).

**2.1.2.2 Efficacy and Registration Studies** Several clinical trials were conducted to test the efficacy and safety of ranibizumab in the treatment of nAMD.

MARINA was a 2-year phase III multicenter study in minimally classic/occult neovascularization to evaluate the efficacy and safety of ranibizumab 0.3 and 0.5 mg compared with sham injections. Best corrected visual acuity (BCVA) significantly improved in the ranibizumab groups compared with controls ($p < 0.001$ for both dosage groups) at month 12 [20, 21].

ANCHOR was an RCT that included classic CNV compared with verteporfin photodynamic therapy (PDT). A clinical benefit in terms of improvement (BCVA) was reported at the 1- and 2-year follow-up (FU) visits [22, 23].

HORIZON was an extension of MARINA and ANCHOR that assessed ranibizumab treatment for 2 additional years and suggested good tolerance for a period ≥ 4 years, although an incremental decline in BCVA improvement was reported [24].

Patients enrolled in these last three studies were also analyzed in SEVEN-UP, a long-term multicenter cohort study that revealed that one-third of patients had poor outcomes, with a visual decline of ≥ 15 letters at year 7 [24, 25].

PIER was another multicenter sham-controlled RCT that tested ranibizumab 0.3 and 0.5 mg. Patients with nAMD were treated quarterly after three monthly loading doses and reported a significant improvement in BCVA at months 12 and 24 ($p < 0.0001$) [26, 27].

Subsequently, HARBOR investigated the efficacy and safety of ranibizumab 0.5 or 2.0 mg administered monthly or PRN in patients with subfoveal nAMD and reported that the PRN regimen and a dose of 0.5 mg resulted in better visual outcomes than monthly ≥ 0.5 mg doses of ranibizumab at month 24 [28].

More recently, T&E was proposed as an alternative strategy to gain similar BCVA results with a significantly lower number of injections than the monthly regimen [29]. These results were also confirmed in CANTREAT at 12 and 24 months (Table 3).

#### 2.1.3 Bevacizumab

**2.1.3.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** Bevacizumab is a fully humanized IgG1 containing the Fc portion; it binds all VEGF-A isoforms and has a molecular weight (Mw) of 148 kDa.

The first indication for intravenous bevacizumab was in metastatic colon cancer; the intravitreal formulation was administered "off label" to treat nAMD and diabetic macular edema (at a much lower dose of 1.25 mg/0.05 mL) [1]. In Italy, it was included in a register of drugs approved for off-label use.

Human studies demonstrated a vitreous $t_{½}$ range of 2.5–7.3 days (mean 4.9 days) following a 1.25 mg/0.05 mL single dose [15]. Other studies reported a serum $t_{½}$ of 18.7 days after three single intravitreal doses, with a serum concentration of 1.58 nM, which is higher than the half-maximal inhibition for VEGF inhibitors of 0.668 nM [16, 17, 36].

Animal studies demonstrated a vitreous $t_{½}$ of 4.32–5.95 days in different rabbit models [37, 38] and a higher concentration in the aqueous humor of the fellow eye than in

**Table 1** Short and full names of trials cited in the article

| Short name | Full name |
|---|---|
| AAVIATE | RGX-314 gene therapy administered in the suprachoroidal space for participants with nAMD |
| ABC | Bevacizumab for nAMD |
| ADAGIO | A depot formulation of sunitinib malate (GB-102) in subjects with neovascular (wet) AMD |
| ALTAIR | Japanese treat and extend study of aflibercept in nAMD |
| ALTISSIMO | A depot formulation of sunitinib malate (GB-102) compared to aflibercept in subjects with wet AMD |
| ANCHOR | Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in AMD |
| Archway | A phase III study to evaluate the port delivery system with ranibizumab compared with monthly ranibizumab injections in participants with wet AMD |
| ASSET | Ranibizumab biosimilar safety efficacy postmarketing |
| AURORA | Assess the safety and efficacy of KH902 in patients with subfoveal choroidal neovascularization secondary to AMD |
| AVANTE | Study assessing the efficacy and safety of intravitreal injections of DE-122 in combination with Lucentis® compared to Lucentis® monotherapy in wet AMD subjects |
| AVENUE | A proof-of-concept study of faricimab (RO6867461) in participants with CNV secondary to AMD |
| BRAMD | Comparing the Effectiveness of Bevacizumab to Ranibizumab in Patients with Exudative Age-Related Macular Degeneration |
| CANTREAT | Canadian Treat-and-Extend Analysis Trial With Ranibizumab in Patients With Neovascular Age-Related Macular Disease |
| CATT | Comparison of AMD treatments trials |
| CEDAR | A Safety and Efficacy Study of Abicipar Pegol in Participants With Neovascular Age-related Macular Degeneration |
| CESAR | Clinical efficacy and safety of Razumab® |
| COAST | Efficacy and safety of intravitreal OPT-302 in combination with aflibercept |
| COLUMBUS-AMD | Efficacy and Safety of the Biosimilar Ranibizumab FYB201 in Comparison to Lucentis in Patients With Neovascular Age-related Macular Degeneration |
| DAVIO | First in Human Study to Evaluate the Safety and Tolerability of EYP-1901 in Patients With Wet Age Related Macular Degeneration |
| DAZZLE | A study to evaluate the efficacy and safety of KSI-301, an anti-VEGF antibody biopolymer conjugate, versus aflibercept in patients with neovascular (wet) AMD |
| DECO | Open-label study of intravitreal ICON-1 in patients with CNV secondary to AMD |
| EMERGE | Study Evaluating Intravitreal hI-con1™ in Patients With Choroidal Neovascularization Secondary to Age-related Macular Degeneration |
| GEFAL | French evaluation group—Avastin versus Lucentis |
| HARBOR | The phase III, double-masked, multicenter, randomized, active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg ranibizumab administered monthly or PRN in patients with subfoveal nAMD |
| HARRIER | Efficacy and safety of RTH258 versus aflibercept—study 2 |
| HAWK | Efficacy and safety of RTH258 versus aflibercept—study 1 |
| HORIZON | Open-label extension trial of ranibizumab for CNV secondary to AMD |
| IVAN | Alternative treatments to inhibit VEGF in age-related CNV |
| LADDER | Study of the efficacy and safety of the ranibizumab port delivery system for sustained delivery of ranibizumab in patients with subfoveal nAMD |
| LUCERNE | A study to evaluate the efficacy and safety of faricimab in participants with nAMD |
| MAGELLAN-AMD | Efficacy and safety of the aflibercept FYB203 biosimilar in comparison to Eylea® in patients with nAMD |
| MANTA | Avastin versus Lucentis in AMD |
| MAPLE | A study to evaluate abicipar pegol for safety and treatment effect in participants with nAMD |
| MARINA | Minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of nAMD |
| OASIS | Safety and tolerability study of suprachoroidal injection of CLS-AX following anti-VEGF therapy in nAMD |
| OPTIC | ADVM-022 intravitreal gene therapy for wet AMD |
| OSPREY | Randomized, active-controlled, phase II study to evaluate safety and efficacy of RTH258, a humanized single-chain anti-VEGF antibody fragment, in patients with neovascular AMD |
| PANDA-1 and -2 | Efficacy and safety trial of conbercept intravitreal injection for nAMD |
| PAVE | A Phase I/II Safety, Tolerability, Immunogenicity, and Bioactivity Study of DE-122 Injectable Solution for Refractory Exudative Age-related Macular Degeneration |
| PHOENIX | A randomized, double-masked, multicenter, sham-controlled, safety and efficacy study of KH902 in patients with wet AMD |

**Table 1** (continued)

| Short name | Full name |
|---|---|
| PIER | A study of rhuFab V2 (ranibizumab) in subjects with subfoveal CNV secondary to AMD |
| RE-ENACT | Real-life assessment of safety and effectiveness of razumab |
| RE-ENACT 2 | A long-term extension of RE-ENACT |
| SEQUOIA | Safety and efficacy of abicipar pegol in participants with nAMD |
| SEVEN-UP | Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON |
| SHORE | Efficacy and safety of intravitreal OPT-302 in combination with ranibizumab |
| STAIRWAY | Study to evaluate faricimab (RO6867461; RG7716) for extended durability in the treatment of nAMD |
| TENAYA | A study to evaluate the efficacy and safety of faricimab in participants with nAMD |
| VIEW 1 and 2 | VEGF Trap-Eye: Investigation of efficacy and safety in wet AMD |
| VISION | A clinical trial to explore safety and efficacy of different doses of pegaptanib sodium, compared to sham, in patients with wet AMD |
| XPLORE | Comparing the efficacy and safety of biosimilar candidate Xlucane versus Lucentis® in patients with nAMD |

*AMD* age-related macular degeneration, *CNV* choroidal neovascularization, *nAMD* neovascular AMD, *VEGF* vascular endothelial growth factor

the vitreous [37]. These results suggested possible systemic circulation through the anterior route, reaching the aqueous and then the vitreous [37].

**2.1.3.2 Efficacy and Registration Studies** The ABC trial was the first prospective multicenter RCT in the UK to compare bevacizumab 1.25 mg (three loading doses with further treatment as needed at 6-week intervals) with standard of care (PDT for predominantly classic CNV; pegaptanib or sham for occult or minimally classic CNV) and reported the superiority of this anti-VEGF drug with improved BCVA on average at week 54 [33].

In CATT, which compared the efficacy and safety of bevacizumab and ranibizumab, bevacizumab was noninferior to ranibizumab in monthly and PRN regimens at 1 and 2 years [30, 31].

Data from a long-term post hoc analysis showed that the visual gain was not maintained at 5 years, although one-half of patients had 20/40 or better BCVA [39].

The IVAN study was a multicenter randomized noninferiority study that compared the efficacy and safety of bevacizumab 1.25 mg and ranibizumab 0.5 mg in patients with nAMD. Enrolled patients were treated with monthly or PRN injections, with a monthly review [39]. Results from the comparison of these drugs were inconclusive, as bevacizumab was neither inferior nor equivalent to ranibizumab in either regimen. The results of other comparative studies such as the BRAMD study, the French GEFAL study, and the Australian MANTA study supported the noninferiority of bevacizumab in comparison with ranibizumab [32, 39–42].

These results confirmed that the use of anti-VEGF was the major long-term therapeutic choice for nAMD [39] (Table 3).

### 2.1.4 Aflibercept

**2.1.4.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** Aflibercept, or VEGF Trap-Eye (EYLEA®; Bayer HealthCare, Berlin, Germany; Regeneron Pharmaceuticals Inc.; Tarrytown, NY, USA), is a 115-kDa recombinant (r-fusion) protein obtained by combining the Fc region of IgG1 with two binding domains of VEGF receptor type 1 and type 2 [1, 10]. Aflibercept traps all isoforms of VEGF-A, VEGF-B, and placental growth factor (PlGF) [10, 43].

Using a mathematical model, a vitreous $t_{½}$ of 7.13 days was estimated [10]. The serum $t_{½}$ for aflibercept was 11.4 days following 3-monthly intravitreal injections of 2 mg/0.05 mL [16, 17]. The peak was achieved within 1–3 days post-dose, and the plasma concentration quickly decreased below the lower limit of quantification [10, 44].

Animal studies showed a vitreous $t_{½}$ of 4.58 and 2.44 days in rabbit and monkey models, respectively [13, 45] (Table 2).

**2.1.4.2 Efficacy and Registration Studies** VIEW 1 and 2 were phase III RCTs evaluating different dose regimens (0.5 mg monthly vs. 2 mg monthly or 2 mg bimonthly after 3 once-monthly loading doses) of aflibercept compared with ranibizumab 0.5 mg monthly [34]. The results from these important studies demonstrated that all aflibercept regimens (and particularly injections every 2 months) were equivalent and demonstrated the noninferiority of aflibercept to ranibizumab in the treatment of nAMD, with fewer injections, reducing treatment burden for patients and caregivers [46].

ALTAIR was another RCT that compared the efficacy and safety of aflibercept in a T&E regimen with two different intervals of adjustment (2 or 4 weeks) [47]. It found improved functional and anatomic outcomes at week 52,

**Table 2** Summary of anti-vascular endothelial growth factor drugs authorized in the EU

| Active substance | Brand name | Date of issue of MA valid throughout the EU | Indications | Mechanism of action | Half-life |
|---|---|---|---|---|---|
| Ranibizumab | Lucentis® | 22 January 2007 | Wet AMD, myopic CNV, DME, RVO, other CNVs | Ranibizumab binds all VEGF-A isoforms, reducing the growth of the blood vessels and controls the leakage and swelling | Vitreous 7.2–9 days [10]; serum 0.5 days after IVT administration that was 90,000 times lower than those in the vitreous [10] |
| Bevacizumab | Avastin® | Off-label | Wet AMD, DME, other indications[a] | Bevacizumab binds all VEGF-A isoforms | Vitreous 2.5 and 7.3 days [10, 15]; serum 18.7 days [10, 15] |
| Aflibercept | Eylea® | 21 November 2012 | Wet AMD, myopic CNV, DME, RVO | Aflibercept traps all isoforms of VEGF-A, VEGF-B, and PlGF | Vitreous 7.13 days [10]; serum 11.4 days [16, 17] |
| Brolucizumab | Beovu® | 13 February 2020 | Wet AMD | Brolucizumab inhibits all isoforms of VEGF-A, developed by grafting complementarity-determining regions of a novel anti-VEGF-A antibody to a human scFv scaffold, with a smaller molecular structure | Vitreous 6 h–3 days [18, 19]; serum 5 days [18, 19] |

*AMD* age-related macular degeneration, *CNV* choroidal neovascularization, *DME* diabetic macular edema, *IVT* intravitreal injection, *MA* marketing authorization, *PlGF* placental growth factor, *RVO* retinal vein occlusion, *scFv* single-chain antibody fragment, *VEGF* vascular endothelial growth factor

[a]Used off label for several indications; some countries, e.g., Italy, have approved it for nAMD and DME

maintained to week 96, with similar results in both treatment groups [47]. In this trial, 60% of patients reached a treatment interval of 12 weeks, and 40% of patients reached a treatment interval of 16 weeks, maintaining efficacy at 12 months (Table 3).

### 2.1.5 Brolucizumab

**2.1.5.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** Brolucizumab (formerly ESBA1008 and RHT258, now Beovu®; Novartis, Basel, Switzerland) is a single-chain antibody fragment that inhibits the VEGF-A isoform. Its molecular structure is smaller (26 KDa) than other anti-VEGF agents, so brolucizumab can be much more concentrated [18, 19]. The serum half-life of brolucizumab is 5 days [18, 19]. Brolucizumab is highly stable and soluble, which allows administration of high doses in a single 50 µL intravitreal injection.

At a dose of 6 mg, its equivalent molar dose is approximately ten times greater than that of aflibercept and approximately 20 times greater than that of bevacizumab and ranibizumab [18, 19]. Preclinical data demonstrated an approximate twofold higher exposure in the retina and RPE/choroid, respectively, with brolucizumab, which may explain its better effect in reducing fluid accumulation in all retinal layers [48] (Table 2).

**2.1.5.2 Efficacy and Registration Studies** A phase II trial, OSPREY, compared brolucizumab 6 mg and aflibercept 2 mg, recording anatomic advantages with brolucizumab and reaching noninferiority in BCVA [35].

Two phase III trials, HAWK and HARRIER, evaluated brolucizumab in two different doses (3 and 6 mg) compared with an aflibercept 2 mg fixed dosage in nAMD. These studies found noninferior outcomes in terms of BCVA and better anatomic outcomes with brolucizumab at week 48 [35]: a more stable central subfield thickness, with fewer unscheduled treatments and better fluid resolution than with aflibercept [19]. HAWK and HARRIER demonstrated that more than half of patients treated with brolucizumab maintained a 12-week regimen in the first year, confirming a longer half-life than aflibercept [35] (Table 3).

**2.1.5.3 Local and Systemic Safety of Marketed Anti-VEGF Drugs** The systemic use of anti-VEGF drugs for the treatment of several cancers has been strongly associated with an increased risk of serious adverse reactions. Whether intravitreal administration of anti-VEGF drugs also carries this risk remains uncertain.

Studies showed that the frequency of severe systemic adverse events (SSAEs), including arterial thromboembolic events and death, was low with intravitreal administration [49]. A recent study explored the risk of systemic adverse

**Table 3** Summary of anti-vascular endothelial growth factor drugs authorized in the EU and registration trials

| Active substance | Study | Study population | Exposure | Outcome | Results |
|---|---|---|---|---|---|
| Ranibizumab | Rosenfeld et al. [20]; MARINA [21, 22] | Age ≥ 50 years; no prior PDT; subfoveal CNV; VA 20/40 to 20/320; total area of CNV ≥ 50% of total lesion area; recent disease progression; lesion size ≤ 12 DA | Patients randomized 1:1:1 to sham or ranibizumab 0.3 or 0.5 mg | Evaluation of efficacy and safety of ranibizumab vs. sham | Ranibizumab associated with clinically and statistically significant benefits in VA and amount of angiographic leakage from CNV in 2 years of FU, with low rates of SAEs |
| | Brown et al. [23]; ANCHOR | Age ≥ 50 years; no prior PDT; subfoveal CNV; VA 20/40 to 20/320; total lesion 5400 µm in greatest linear dimension (~ 9 DAs) | Randomized 1:1:1 to PDT or ranibizumab 0.3 or 0.5 mg | ITT efficacy analysis was at 12 months, with continued measurements to month 24<br>% losing < 15 letters from baseline VA<br>% gaining > 15 letters from baseline<br>AEs monitored | At months 12 and 24, the VA benefit from ranibizumab was statistically significant ($P < 0.0001$ vs. PDT) and clinically meaningful |
| | Singer et al. [24]; HORIZON | Included patients who were randomized to treatment with ranibizumab in MARINA, ANCHOR | Patients treated with ranibizumab in the initial study; patients randomized to control who crossed over to receive ranibizumab; ranibizumab-naïve patients | BCVA assessed as part of the eye examination on ETDRS at a starting test distance of 2 meters | Good tolerance of ranibizumab for a period ≥4 years, though reporting an incremental decline in BCVA improvement |
| Bevacizumab/ranibizumab | CATT research group [30, 31] | Age ≥ 50 years; VA 20/25 to 20/320; on OCT the presence of leakage and fluid | Intravitreal injections of ranibizumab or bevacizumab on a monthly schedule or as needed with monthly evaluation | Mean change in BCVA at 1 year | Mean BCVA improved by 9.2 and 10.5 letters in the monthly and TREX cohorts, respectively ($P = 0.60$). Rate of SSAEs was higher with bevacizumab than with ranibizumab (24.1 vs. 19.0%) |
| | Chakravarthy et al. [32]; IVAN | Age ≥ 50 years; BCVA ≥ 25 letters | Randomized 1:1:1:1 to intravitreal injections of ranibizumab or bevacizumab in continuous or discontinuous regimens | Primary outcome: BCVA at 2 years<br>Primary safety outcome: arterial thrombotic event/heart failure | Ranibizumab and bevacizumab had similar efficacy. Reduction in the frequency of retreatment resulted in a small loss of efficacy. Safety was worse when treatment was administered discontinuously |
| Bevacizumab | Tufail et al. [33]; ABC | Age ≥ 50 years; total lesion 12 (DAs); BCVA of 6/12 to 6/96 | Randomized 1:1 to intravitreal bevacizumab or standard NHS care or sham | Proportion of patients gaining > 15 letters of VA at 1 year (54 weeks) | Bevacizumab patients gained >15 letters from baseline more frequently vs. standard care group ($P < 0.001$) |
| Aflibercept | Heier et al. [34]; VIEW | Age ≥ 50 years; CNV comprising > 50% of total lesion size; BCVA between 20/40 and 20/320 Snellen equivalent | Randomized to intravitreal aflibercept 0.5 mg monthly, 2 mg monthly, 2 mg every 2 months after three initial monthly doses, or ranibizumab 0.5 mg monthly | Proportion of patients maintaining vision at week 52 | All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary endpoint |

**Table 3** (continued)

| Active substance | Study | Study population | Exposure | Outcome | Results |
|---|---|---|---|---|---|
| Brolucizumab | Dugel et al. [35]; HAWK | Age ≥ 50 years; total lesions comprising > 50% of total lesion area; IRF and/or SRF; BCVA between 20/32 and 20/400 | Patients randomized to intravitreal brolucizumab 3 or 6 mg or aflibercept 2 mg | BCVA change from baseline to week 48 (margin: four letters) | At week 48, each brolucizumab arm demonstrated noninferiority to aflibercept in BCVA change from baseline (LSM +6.6 [6 mg] and +6.1 [3 mg] letters with brolucizumab vs. +6.8 letters with aflibercept) |
| | Dugel et al. [35]; HARRIER | | Eyes randomized 1:1 to brolucizumab 6 mg or aflibercept 2 mg | | At week 48, each brolucizumab arm demonstrated noninferiority to aflibercept in BCVA change from baseline + 6.9 (brolucizumab 6 mg) vs. +7.6 (aflibercept) letters |

*BCVA* best corrected visual acuity, *CNV* choroidal neovascularization, *DA* disk area, *ETDRS* Early Treatment for Diabetic Retinopathy Study, *FU* follow-up, *IRF* intraretinal fluid, *ITT* intention to treat, *LSM* least squares mean, *NHS* national health service, *OCT* optical coherence tomography, *PDT* photodynamic therapy, *SAE* serious adverse event, *SRF* subretinal fluid, *SSAE* severe systemic adverse event, *VA* visual acuity

[a]Refer to Table 2 for the full names of studies cited in this table

events (AEs) after intravitreal bevacizumab, ranibizumab, and aflibercept in routine clinical practice and reported no differences in acute myocardial infarction, cardiovascular diseases, major bleedings, or hospitalization for all causes between the drugs [50].

More recently, using the Italian spontaneous reporting system [51], it was possible to provide an overview of the safety of anti-VEGF drugs in eye care settings. Specifically, of 2472 anti-VEGF drug-related reports, 299 (12.1%) were attributed to intravitreal use of these drugs. Most serious adverse drug reactions related to anti-VEGF drugs in patients with cancer are known and clinically relevant (e.g., gastrointestinal and vascular disorders). The frequency of reported serious adverse drug reactions was higher for intravitreal than for systemic use of anti-VEGF drugs in patients with cancer (58.9 vs. 34.1%; $p < 0.001$) and were disproportionally associated with ischemic heart disease and thromboembolic and cerebrovascular events.

In addition, VEGF regulates several features of the central nervous system, particularly in dopaminergic neurons, so that its inhibitors seem to be linked to Parkinson-like events and dementia. Two recent case reports described a potential link between intravitreal anti-VEGF use and Parkinson's disease and dementia [52–54]. In a more recent study using VigiBase, a potential signal of an AE emerged as analyzing disproportionality by the preferred term "Parkinson's disease" ($N = 6$ individual case safety reports; proportional reporting ratio 3.05 [95% confidence interval 1.36–6.81]) after intravitreal use of ranibizumab, which requires further investigation [52–54].

The adverse ocular effects with ranibizumab included endophthalmitis (from 0.5 to 0.9% at year 1 and 2, respectively), uveitis or other ocular inflammation, retinal and vitreous hemorrhages, elevated intraocular pressure (IOP) > 30 mmHg (ranging from 7.6% in the first year to 17.8% in the second year of treatment), and cataract compared with controls [55]. Similarly, the rates of serious ocular AEs at 1 and 2 years with bevacizumab were similar to those with ranibizumab for endophthalmitis, retinal detachment, traumatic cataract, and RPE tears, with bevacizumab having a higher rate of severe uveitis [31]. As reported in the post hoc analysis of CATT, ranibizumab and bevacizumab were both associated with an increased risk of developing geographic atrophy at 2-year FU (21 vs. 17%, respectively), specifically in case of monthly treatments versus a PRN regimen (24 vs. 15%, respectively) [39]. The incidence of ocular AEs with aflibercept was comparable to that with the other anti-VEGF drugs or were related to the injection procedure [55]. Data from pivotal studies reported brolucizumab was well-tolerated, with overall safety similar to that of aflibercept [35]. In the brolucizumab safety profile analysis, interesting AEs included uveitis and iritis (mild and moderate forms treated with topical corticosteroids; most

resolved without any sequelae) [35, 56] and more severe cases of occlusive retinal vasculitis (RV) [55]. Specifically, intraocular inflammation was identified in 50 (4.6%) of the brolucizumab-treated patients in pivotal studies, among whom 36 (3.3%) had concomitant RV. The American Society of Retina Specialists conducted a post-approval analysis of brolucizumab-associated intraocular inflammation cases and concluded that, despite the risk of vision loss associated with RV following brolucizumab injection, the overall rate of vision loss in the study population was not different between the brolucizumab and aflibercept arms in HAWK and HARRIER [57]. On 27 May 2021, a notification of urgent safety measures in response to the increased incidence of intraocular inflammation (IOI) and related AEs, including RV and retinal vascular occlusion, in patients receiving doses every 4 weeks beyond the first three doses ("loading phase") in nAMD was released, and studies with these regimens were terminated early (data on file; MERLIN first interpretable results. Novartis; 2021).

## 2.2 Non-EU-Approved Anti-VEGF Drugs

### 2.2.1 Conbercept

**2.2.1.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** Conbercept (KH902) (Lumitin; Chengdu Kanghong Biotech Co, Ltd, Chengdu, China) is a 141-kDa engineered fusion protein produced by the gene recombination of VEGF receptor domain with Fc fragment of human Ig [58]. It is approved only in China in 2013 to treat nAMD [58]. Conbercept blocks all isoforms of VEGF-A, VEGF-B, VEGF-C, and PlGF [19, 59].

Animal studies reported a serum $t_{½}$ of 4–5 days in monkey models [60]. During animal experiments, conbercept had a longer $t_{½}$ and greater bioavailability than ranibizumab. In fact, the most relevant focus was to test the efficacy of conbercept in patients with nAMD using a less frequent maintenance dosing interval regimen [58].

**2.2.1.2 Efficacy and Registration Studies** The phase II AURORA study assessed the safety and efficacy of conbercept 0.5 versus 2.0 mg monthly or PRN in patients with nAMD and reported that the treatment was well-tolerated at month 12 [61].

The Chinese registration phase III study (PHOENIX) was a 12-month prospective RCT that enrolled patients with nAMD, including polypoidal choroidal vasculopathy without subfoveal atrophy or scarring. The treatment protocol regimen was as follows: the conbercept group received a loading dose of conbercept 0.5 mg every month for 3 months then an injection every 3 months until month 12; the sham group received no injections in the first 3 months, then conbercept was administered monthly for 3 months, followed by an injection every 3 months until month 12 [58].

At month 3 in the conbercept group, 49.4% of patients gained ≥ 10 letters and 23.5% gained ≥ 15 letters in BCVA, with a significant improvement in anatomic outcomes compared with sham; at month 12, no statistically significant differences were reported for functional or anatomic outcomes.

Two other phase III RCTs are ongoing: PANDA-1 and PANDA-2 (randomized quadruple-blinded multicenter studies) are comparing conbercept 0.5 or 1.0 mg versus aflibercept 2.0 mg, respectively. In these studies, after the first two monthly doses, patients with nAMD receive doses every 2 months for 36 weeks [62]. In April 2021, the week-36 primary endpoint evaluation for the PANDA global clinical studies was available, and the desired primary endpoint was not met in either PANDA study. The analysis showed that no safety signals were detected. After consultation with the steering committee, Kanghong discontinued the PANDA studies.

**2.2.1.3 Safety** Conbercept was well-tolerated intravitreally, and the PHOENIX study reported similar rates of ocular and systemic AEs for both treated and sham groups, and no serious AEs (SAEs) were reported. The most common ocular AEs were increase in IOP and conjunctival hemorrhage. The large molecular size of conbercept limits the permeability through blood–ocular barriers, reducing systemic exposure [58]. Interestingly, conbercept seemed to reduce the plasma level of VEGF more effectively than did ranibizumab [59].

A recent systematic review reported that conbercept produced a change in BCVA similar to that of ranibizumab at 3-month FU, with a better reduction in central retinal thickness (CRT), probably due to the different molecular target of these two molecules [59].

### 2.2.2 Abicipar

**2.2.2.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** Abicipar pegol (AGN-150998, MP0112; Allergan plc, Dublin, Ireland/Molecular Partners, Switzerland) is an anti-VEGF molecule based on the designed ankyrin repeat proteins (DARPin) family, binding VEGF-A [62]. DARPin molecules are designed to be smaller with high selectivity and to be active at lower concentrations with increased stability, affinity, and specificity [55, 56].

The specific molecular characteristics include the low Mw (only 34 kDa, consisting of a recombinant DARPin protein of 14 kDa plus a 20 kDa polyethylene glycol portion) and the high target-binding affinity ($K_d$ 1–4 pmol/L) [55, 63]. The $t_{½}$ in aqueous humor was 13 days, longer than that of ranibizumab [19].

**2.2.2.2 Efficacy and Registration Studies** Phase II and III studies compared abicipar with ranibizumab, in particular in the parallel, randomized, double-masked, multicenter CEDAR and SEQUOIA trials, which compared two different dosing interval regimens of abicipar 2.0 mg (every 8 weeks [Q8W] and every 12 weeks [Q12W]) versus ranibizumab 0.5 mg monthly (Q4W) through week 96, in treatment-naïve patients with nAMD. Abicipar maintained stable vision in > 91% of patients receiving the Q12W regimen [62], and BCVA improvement was sustained during the second year [64, 65]. The mean CRT was significantly reduced in all treatment groups in the first year, and only four intravitreal injections of abicipar were required to maintain anatomical benefit in the second year [64, 65].

**2.2.2.3 Safety** CEDAR and SEQUOIA revealed a higher IOI, such as uveitis, vitreitis, and RV, and a higher incidence of endophthalmitis in the abicipar group compared with ranibizumab for both treatment doses. In detail, intraocular inflammation in the study eye was reported for 96 patients (15.4%) in the abicipar Q8W group, 96 patients (15.3%) in the abicipar Q12W group, and two patients (0.3%) in the ranibizumab Q4W group. As this effect may have been due to molecular impurities in the manufacturing of DARPin, another reformulated agent was used in the phase II MAPLE trial to test the safety of this molecule [62]. The improved manufacturing process led to an IOI of 8.9%, which was lower than that observed in the previous phase III studies.

Considering all these data, the US FDA considered the benefit:risk ratio unfavorable in terms of the rate of ocular inflammation with the use of abicipar pegol 2 mg/0.05 mL in patients with nAMD [55].

### 2.2.3 Pegpleranib

**2.2.3.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** Pegpleranib (Fovista; Ophthotech Corp., New York, NY, USA) is a platelet-derived growth factor (PDGF) inhibitor that blocks the interaction between PDGF and its receptor. It was administered with other anti-VEGF agents (ranibizumab, bevacizumab, or aflibercept), and this combined mechanism could act on the vascular wall and particularly on pericytes, allowing a better response to anti-VEGF [66].

**2.2.3.2 Efficacy and Registration Studies** Despite encouraging results from phase II studies, which reported a 62% benefit versus anti-VEGF, data from the phase III trial showed no statistically significant differences in BCVA between monotherapy or combined groups [19]. The addition of pegpleranib 1.5 mg to an aflibercept or bevacizumab regimen did not result in benefit as measured by the mean change in BCVA at the 12-month time point.

## 2.3 Agents under Investigation

### 2.3.1 Faricimab

**2.3.1.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** Faricimab (formerly RG7716; Roche/Genentech) is a bi-specific antibody that blocks VEGF-A and angiopoietin-2 (Ang-2). Levels of Ang-2 are elevated during nAMD, so simultaneous blockage of Ang-2 may lead to magnification of the anti-inflammatory effect [62]. Its molecular structure contains a modified Fc portion protecting against systemic absorption and intraocular inflammation [56].

**2.3.1.2 Efficacy and Registration Studies** STAIRWAY was a phase II noninferiority study evaluating faricimab 6 mg (Q4W × 4 doses, then Q12W and Q16W) compared with ranibizumab 0.5 mg Q4W. It reported similar BCVA results between groups at week 52 [56, 62]. The protocol provided that patients in the Q16W regimen at week 24 could be switched to Q12W dosing according to predefined activity criteria; the analysis of results reported that, at week 24, 65% of patients had no disease activity [55], suggesting a sustained long interval dose regimen effect for the majority of patients.

Another phase II randomized double-masked multicenter study, AVENUE, enrolled treatment-naïve patients with nAMD and evaluated ranibizumab 0.5 mg Q4W and Q4W × 3 followed by faricimab 6 mg Q4W, respectively, compared with faricimab in different doses and interval regimens: faricimab 1.5 mg Q4W or 6 mg Q4W and Q4W × 4 followed by Q8W. In all arms, a significant reduction of CRT was reported, which was more relevant in the combination arm, leading to conclusions about the efficacy and safety of faricimab Q4W and Q8W compared with ranibizumab Q4W [62].

Two phase III triple-masked parallel RCTs, TENAYA and LUCERNE, are currently exploring faricimab Q16W versus aflibercept Q8W [56, 62]. On 25 January 2021, Roche announced that both studies had met their primary endpoints and showed that people receiving faricimab injections at fixed intervals of up to Q16W achieved visual acuity outcomes that were noninferior to those receiving aflibercept injections Q8W. Nearly half (45%) of people in both studies were treated with faricimab Q16W during the first year with a good safety profile. The nAMD open-label extension study is ongoing.

**2.3.1.3 Safety** Phase II studies reported no significant differences in terms of AEs between faricimab and other anti-VEGF agents [56] (Table 4).

### 2.3.2 Port Delivery System

**2.3.2.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** The port delivery system (PDS) (Genentech) is a novel permanent refillable drug reservoir that releases ranibizumab from a device surgically placed in the pars plana [19, 56, 62].

The mechanism of action of this device is a sustained release of anti-VEGF agent for passive diffusion from the implant into the vitreous [62]. This kind of device may reduce patient treatment burden by avoiding monthly injections.

**2.3.2.2 Efficacy and Registration Studies** The phase II LADDER study was an RCT that tested the efficacy and safety of this device in patients with nAMD, evaluating ranibizumab in PDS (10, 40, and 100 mg/mL) compared with monthly ranibizumab 0.5 mg intravitreal injections, respectively. The results from the PDS 100 mg/mL arm seemed to be comparable to those from the intravitreal ranibizumab arm [67, 68].

The phase III Archway study evaluated fixed-interval dosing: the PDS was refilled every 24 weeks with ranibizumab 100 mg/mL and compared with monthly injections of ranibizumab 10 mg/mL. Results demonstrated that 98.4% of patients using the PDS were able to go 6 months without needing additional treatment and achieved vision outcomes equivalent to patients receiving monthly ranibizumab eye injections, a current standard of care. In the study, PDS was generally well-tolerated, with a favorable benefit–risk profile. A phase IIIb study (MR42410) on the effectiveness and safety of a 36-week refill regimen for the PDS with ranibizumab versus aflibercept T&E in nAMD Q16W is ongoing.

**2.3.2.3 Safety** The rate of vitreous hemorrhage was high during the surgical procedure (almost 50%). A novel surgical approach was tested to reduce this ocular AE, involving a scleral dissection to the pars plana followed by cauterization of the choroid, reducing the rate of postoperative vitreous hemorrhage to 4.5% [62]. No long-term studies were available to evaluate the local effects and durability of the implant (Table 4).

### 2.3.3 OPT-302

**2.3.3.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** OPT-302 (OPTHEA Ltd.; Melbourne, Australia) is a VEGF-C/D inhibitor molecule. Reports from animal studies indicated beneficial effects in conjunction with other anti-VEGF drugs (binding VEGF-A) for the concomitant blockage of different isoforms of VEGF [62].

**2.3.3.2 Efficacy and Registration Studies** Data from phase I/II studies reported the noninferiority of OPT-30 as monotherapy or in combination with other anti-VEGF drugs [69].

In the phase II study (NCT03345082), patients with nAMD were randomized to receive OPT-302 2 mg + ranibizumab 0.5 mg or OPT-302 0.5 mg + ranibizumab 0.5 mg or ranibizumab 0.5 mg alone. Phase II studies showed that the combination of OPT-302 + ranibizumab determined a significant improvement in BCVA, retinal fluid reduction, and lesion area at week 24 compared with ranibizumab monotherapy [62].

Two different phase III RCTs are currently evaluating the efficacy and safety of intravitreal OPT-302 in combination with aflibercept (COAST) or ranibizumab (ShOre) in patients with nAMD.

**2.3.3.3 Safety** Safety data reported no differences between OPT-302 + ranibizumab compared with ranibizumab monotherapy (Table 4).

### 2.3.4 KSI-301

**2.3.4.1 Molecular Characteristics, Pharmacodynamics, and Pharmacokinetics** KSI-301 (Kodiak Sciences; Palo Alto, CA, USA) is an anti-VEGF antibody polymer conjugate of humanized anti-VEGF monoclonal antibody; the presence of a phosphorylcholine-based polymer increases the stability. The molecular characteristics consist of ameliorated pharmacokinetics, with greater long-term concentration and bioactivity than standard of care [62].

**2.3.4.2 Efficacy and Registration Studies** DAZZLE is an ongoing phase IIb/III randomized, double-masked, prospective study evaluating the efficacy and the safety of KSI-301 in treatment-naïve patients with nAMD compared with standard of care. Patients will receive KSI-301 5 mg in an individualized regimen every 12, 16, and 20 weeks after a monthly loading dose versus aflibercept 2 mg Q8W after three monthly loading doses [70].

**2.3.4.3 Safety** No SAEs were reported, and phase I studies reported primary safety and good tolerability [62] (Table 4).

### 2.3.5 ADVM-022

ADVM-022 (AAV.7m8-aflibercept) is a recombinant, replication-deficient adeno-associated virus (AAV.7m8) gene therapy vector carrying a coding sequence for aflibercept. The phase I OPTIC trial and its long-term extension are currently active in patients with nAMD. Preliminary results showed that the patients in cohort 1 ($6 \times 1011$ vg/eye) did not need any supplemental injections for $\geq$ 15 months.

**Table 4** Summary of anti-VEGF drugs under investigation (phase III trials)

| Active substance | Study type | Outcome | Status |
|---|---|---|---|
| Faricimab | TENAYA: a phase III multicenter, randomized, double-masked, active-comparator-controlled study evaluating the efficacy and safety of faricimab in patients with nAMD | Average change from baseline BCVA at week 48/over time | Ongoing |
| | LUCERNE: a phase III multicenter, randomized, double-masked, active-comparator-controlled study evaluating the efficacy and safety of faricimab in patients nAMD | Average change from baseline in BCVA at week 48 (timeframe: baseline up to 48 weeks) | Enrolling by invitation |
| OPT-302 | COAST: a phase III multicenter, double-masked, randomized study evaluating the efficacy and safety of intravitreal OPT-302 plus aflibercept vs. aflibercept alone in patients with nAMD | Mean change in BCVA (timeframe: baseline to week 52) | Ongoing |
| | ShOre: a phase III multicenter, double-masked, randomized study evaluating the efficacy and safety of intravitreal OPT-302 plus ranibizumab vs. ranibizumab alone in participants with nAMD | | |
| KSI-301 | DUZZLE: a phase IIb/III prospective, randomized, double-masked, active-comparator-controlled, multicenter study investigating the efficacy and safety of repeated intravitreal administration of KSI-301 in subjects with nAMD | Mean change in BCVA from day 1 (timeframe: year 1) | Ongoing |
| PDS | Archway: a phase III randomized, multicenter, open-label (visual assessor-masked), active-comparator study assessing the efficacy, safety, and pharmacokinetics of ranibizumab 100 mg/mL via PDS vs. ranibizumab 0.5 mg (10 mg/mL) intravitreal injections in patients with nAMD | Change from baseline in BCVA score at the average of week 36 and week 40 (timeframe: baseline to week 40) | Completed |

*BCVA* best corrected visual acuity, *nAMD* neovascular age-related macular degeneration, *PDS* port delivery system

Patients in the low-dose cohorts 2 and 3 ($2 \times 1011$ vg/eye) required a few rescue injections, and the safety profile was acceptable [71, 72].

#### 2.3.6 RGX-314

RGX-314 (Regen BioPharma; La Mesa, CA, USA) uses a novel AAV8 vector to deliver a genome that induces the production of an anti-VEGF Fab, similar to ranibizumab, delivered with vitrectomy and subretinal injection.

The phase II randomized dose-finding trial (AAVIATE) aims to evaluate the efficacy and safety of RGX-314 gene therapy in subjects with nAMD. Approximately 40 participants were planned to be enrolled into two cohorts with different doses in comparison with ranibizumab.

#### 2.3.7 GB-102

GB-102 (GrayBug Vision; Redwood City, CA, USA) is an injectable form of sunitinib maleate, a tyrosine kinase inhibitor (TKI) that targets VEGF-A, PDGF, and many other kinases [73]. When injected, it forms a depot in the inferior vitreous that gradually biodegrades over time. Available data supported the finding that GB-102 treatment can last up to 6 months with stable visual acuity and retinal thickness outcomes before another dose is necessary.

ADAGIO (NCT03249740) was a phase I/IIa open-label single-dose trial of GB-102 in patients with nAMD that met the primary endpoints of safety and tolerability.

ALTISSIMO is an ongoing phase IIb (NCT03953079) randomized single-masked controlled study evaluating the safety and duration of effect of GB-102 as measured by time to first rescue treatment across several dose levels of GB-102 administered every 6 months as compared with intravitreal aflibercept administered every 2 months in subjects with nAMD who have received prior induction with anti-VEGF. According to the preliminary results, nAMD eyes treated with the 2-mg dose were all switched to the 1-mg dose of GB-102.

#### 2.3.8 EYP-1901

EYP-1901 is a potential twice-yearly sustained-delivery intravitreal anti-VEGF treatment for nAMD. EYP-1901 combines a bioerodible formulation of EyePoint's proprietary Durasert® sustained-release technology with vorolanib,

a TKI. Vorolanib provided clear efficacy signals in two prior human trials in nAMD as an orally delivered therapy with no significant ocular AEs. The phase I DAVIO open-label dose-escalation trial will examine 13 patients who were responsive to previous anti-VEGF treatments with a single intravitreal injection of EYP-1901 [74].

#### 2.3.9 CLS-AX

Axitinib is a TKI currently approved to treat renal cell cancer that achieves pan-VEGF blockade, directly inhibiting VEGF receptors 1, 2, and 3 with high potency and specificity. CLS-AX (axitinib injectable suspension) was administered by suprachoroidal injection via Clearside's SCS Microinjector in six patients with wet AMD in a phase I/II open-label dose-escalation OASIS trial. The trial is ongoing [75].

#### 2.3.10 PAN-90806

PAN-90806 (PanOptica; Mount Arlington, NJ, USA) is a TKI of VEGF-A and PDGF. This drug is delivered topically as eye drops that use the transscleral vascular route to reach the target tissues in the retina.

A phase I study confirmed the efficacy of the topical treatment. However, punctate keratopathy was a common adverse effect. The formulation was modified, and a subsequent phase I/II randomized, double-masked, uncontrolled study in treatment-naïve patients with nAMD using PAN-90806 topical drops found "no major or serious untoward (unfavorable and unintended) safety issues or trends" [76].

#### 2.3.11 ICON-1

ICON-1 (Iconic Therapeutics; South San Francisco, CA, USA) is a recombinant modified factor VIIIa protein linked with the Fc portion of a human IgG1. It binds to tissue factor, which is overexpressed in CNV, but does not interfere with normal blood coagulation. A phase I open-label dose-escalation nonrandomized study of intravitreal injection of ICON-1 was performed in patients with nAMD ($n = 18$) [77, 78]. The primary endpoint of safety and tolerability was met, as no patients had any drug-related SAEs.

EMERGE was a phase II randomized double-masked study of intravitreal injections in patients with nAMD ($n = 88$) [77, 78], who were randomized to a combination of ranibizumab 0.5 mg and ICON-1 0.3 mg, ranibizumab 0.5 mg only, or ICON-1 0.3 mg only for 3 months. CNV decreased by 40% in the combination arm, 14.6% in the ranibizumab-only arm, and 17.2% in the ICON-1-only arm at 6 months, with the same improvement in BCVA and reduction of CRT in all groups. DECO (NCT03452527) was a phase II randomized open-label parallel study in patients with nAMD ($n = 15$). All patients received initial treatment with aflibercept and then maintenance therapy with intravitreal injection of ICON-1 0.6 mg or intravitreal injection of aflibercept 2 mg.

#### 2.3.12 AKST4290

AKST4290 (formerly ALK4290; Alkahest; San Carlos, CA, USA) is an oral treatment that targets eotaxin, an immunomodulatory chemokine that is highly expressed in choroidal endothelial cells and in the circulation in patients with nAMD. The agent is an inhibitor against the natural receptor for eotaxin (CCR3). AKST4290–201 (NCT03558061) and AKST4290–202 (NCT03558074) were both phase IIa single-arm open-label studies of oral AKST2490 400 mg (twice daily) monotherapy in treatment-naïve patients with nAMD who no longer responded to anti-VEGF. AKST4290–201 and AKST4290–202 showed that 83 and 72% of patients, respectively, had stable or better BCVA at 6 weeks, with good safety. The PHTHALO-205 study was planned to evaluate the efficacy and safety of AKST4290 in combination with aflibercept injections in treatment-naïve subjects with nAMD.

#### 2.3.13 DE-122

DE-122 (Carotuximab; Santen; Osaka, Japan/TRACON Pharmaceuticals; San Diego, CA, USA) is an antibody that binds endoglin, a protein with a critical role in angiogenesis. This drug is an ophthalmic reformulation of TRC 105, an anticancer drug made by TRACON.

PAVE (NCT02555306) was a phase I/II open-label dose-escalating sequential-cohort study of intravitreal DE-122 in patients with nAMD ($n = 12$) who were refractory to VEGF inhibitors. The study explored different doses and found an approximate two- or three-letter improvement and a 0.36–0.116 micron thickness reduction in the new drug arms. No medication-related SAEs had been observed at 90 days.

AVANTE (NCT03211234) is an ongoing phase II multicenter randomized double-masked active-control study of intravitreal injections of DE-122 in patients with nAMD ($n = 76$). Patients were randomized 1:1:1 to arms that received either DE-122 with ranibizumab, high-dose DE-122 with ranibizumab, or ranibizumab alone.

## 3 Biosimilar Anti-VEGF Drugs

A biosimilar is a copy of a biological agent defined as "a medical product with a similar safety, efficacy and quality as an already authorized biologic product" [79]. Since 2006 in Europe, biosimilar drugs have been marketed to improve

access to care by offering biological drugs that are not clinically different from the originator, at a lower price, which is even more beneficial in developing countries [79, 80].

The overall cost and time for development and final marketing approval for a biosimilar is much less than for the originator; nevertheless, biosimilars undergo extensive pre-marketing comparability exercises with their originator, as required by regulatory authorities [81].

Recently, biosimilars of anti-VEGF agents were introduced for the treatment of retinal vascular diseases.

### 3.1 Ranibizumab Biosimilar Drugs

To date, there are seven biosimilars of ranibizumab.

Razumab® (Intas Pharmaceuticals Ltd; Ahmedabad, GJ, India) was the world's first biosimilar to ranibizumab and was approved in 2015 by the Drug Controller General of India for the treatment of nAMD [80, 82]. A head-to-head study compared the efficacy and safety of razumab with that of innovator ranibizumab and showed similar relative binding and potency with some differences in the serine and asparagine sequences [83].

Two important retrospective multicenter observational studies, RE-ENACT and RE-ENACT 2 (a long-term extension of RE-ENACT), tested the use of this molecule in the treatment of retinal vascular disorders in a real-world setting, making conclusions about the safety and efficacy of this drug [80–82]. The RE-ENACT study enrolled 561 eyes affected by AMD, diabetic macular edema, and retinal vein occlusion for a FU period of 12 weeks; in the RE-ENACT 2 study, 341 eyes were enrolled with 48 weeks of FU, including eyes affected by myopic CNV [80, 82].

Data from the CESAR study showed a rapid BCVA improvement and reduction in retinal thickness, with efficacy observed as early as 1 month and maintained until 3 months [84].

These studies reported encouraging results in terms of improvement in BCVA accompanied by a stabilization or reduction of retinal thickness in patients with nAMD treated with razumab at weeks 12 and 48; the subgroup analysis found no differences related to lesion type [80].

The retrospective and real-life nature of these studies represented the major limitations. The ocular AEs were generally similar to those with ranibizumab, but a higher incidence of sterile intraocular inflammation was reported, probably due to a higher endotoxin level; for this reason, the molecule was revised by the manufacturer [80].

The prospective, multicenter ASSET study enrolled 126 patients with nAMD to receive intravitreal razumab 0.5 mg monthly for 24 weeks and tested the immunogenicity of this molecule; no AEs suggestive for immunogenicity were noted during the 6-month FU period [85].

Data from a major clinical real-world study were recently published. This study analyzed 6404 eyes treated with intravitreal injections of Razumab over 4.25 years for several retinal vascular diseases, including nAMD (15.29%), and with different treatment regimens (PRN or T&E) [86]. This important long-term FU study reported that the most common ocular AEs (1978 events/9406 injections performed during the study period) were subconjunctival hemorrhage (8.2%), transient blurring of vision (6.5%), and mild ocular pain (5.27%) and rare cases of raised IOP (0.33%), RPE tear (0.33%), mild anterior uveitis (0.1%), vitreitis (0.02%), and endophthalmitis (0.01%), with an incidence similar to that with ranibizumab. The incidence of nonfatal myocardial infarction and nonfatal cerebrovascular accident was 0.12 and 0.09%, respectively [86].

The following six biosimilars to ranibizumab have reached phase III studies.

- R TPR 024 (Reliance Life Sciences Pvt Ltd; Navi Mumbai, MH, India) has completed the prospective multicenter double-masked phase III RCT, enrolling 159 patients with nAMD. This study compared R TPR 024 or innovative ranibizumab injected monthly for 24 weeks [81].
- Lupin Ltd (Mumbai, India) started a phase III trial of ranibizumab that is ongoing to assess BCVA changes at week 8 during a treatment regimen of monthly injections for 3 months [81].
- FYB201 (Formycon AG/Bioeq; Germany) has completed the COLUMBUS-AMD study, a quadruple-masked multicenter phase III trial comparing BCVA changes between groups with a FU period of 8 weeks. Similar efficacy between FYB201 and innovator ranibizumab was reported [81]. The data were resubmitted to the FDA for approval.
- Xlucane (Xbrane Biopharma; Solna, Sweden) is being evaluated in the ongoing XPLORE phase III trial, a multicenter double-masked trial involving 580 nAMD eyes and analyzing changes in BCVA at week 8 between Xlucane or innovator ranibizumab administered monthly until 52 weeks [81].
- SB11 (Byooviz; Samsung Bioepis Co Ltd; Incheon, South Korea) is being tested in a quadruple-masked multicenter phase III trial evaluating the pharmaceutical profile, immunogenicity, efficacy, and safety versus that of innovator ranibizumab in 705 patients with nAMD with a FU period of 52 weeks [81, 87]. Patients received SB11 0.5 mg or ranibizumab 0.5 mg intravitreally every 4 weeks for 48 weeks; the primary endpoints were BCVA changes from baseline to week 8 and anatomical features at week 4. Data to week 24 were recently published, and SB11 demonstrated equivalence for both primary end-

points with safety and immunogenicity profiles similar to those of reference ranibizumab [87]. Ad interim data on a small sample showed a rate of endophthalmitis similar to that with ranibizumab [86]. On 23 August 2021, the European Commission approved Byooviz, which will be sold in the EU by Biogen [88].

– SJP-0133 (Senju Pharmaceuticals; Osaka, Japan) will complete the single-masked phase III RCT in 2022. In this study, patients are receiving three monthly injections of SJP-0133 or innovator ranibizumab followed by a particular PRN regimen from week 12 to week 48 instead of a fixed regimen, unlike the other drugs [81].

### 3.2 Bevacizumab Biosimilar Drugs

Bevacizumab biosimilars are already approved for clinical use in different countries after completion of phase III studies. In 2016, the Drug Controller General of India approved the following molecules: Cizumab (Hetero; Hyderabad, India), BevaciRel (Reliance Life Science; Mumbai, India), Zybev® (Zydus Cadilla; Ahmedabad, India), Bevatas® (Intas Pharmaceuticals; Ahmedabad, India), KRABEVA (Biocon; Bengaluru, India) [89]. The most used in ophthalmology were Zybev® and BevaciRel, which are less often used off label by retina specialists, as reported by the Vitreo-Retinal Society—India (VRSI), before the introduction of ranibizumab biosimilar drugs [90]. In Europe and the USA, ABP215 (MVASI; Allergan; Dublin Ireland/Amgen; Thousand Oaks, CA, USA) was approved in 2017 [89]. Two other bevacizumab biosimilar molecules were approved by the Russian regulatory body in 2015 and by the Argentina regulatory body in 2016: BCD-021 (Biocad; Saint Petersburg, Russia) and mAbxience (mAbxience; Madrid, Spain), respectively [89].

Recently, encouraging results with the use of Strivant® (CinnaGen Co., Iran), another bevacizumab biosimilar drug, in terms of BCVA and improved anatomical features were reported in a case series recruiting patients affected by several retinal disorders, including nAMD [91].

### 3.3 Aflibercept Biosimilar Drugs

To date, three biosimilars to aflibercept are being evaluated in phase III clinical trials for nAMD.

In Europe, FYB203 (Formycon AG; Munich, Germany/Bioeq GmbH; Holzkirchen, Germany) is being compared with innovator aflibercept in the MAGELLAN-AMD phase III study enrolling 400 patients with nAMD [81]. The study started in August 2020 with the objective of providing data for the efficacy, safety, and immunogenicity of FYB203 [92].

In the USA, ABP-938 (Amgen) is being evaluated for nAMD in a multicenter RCT comparing ABP-938 or innovator aflibercept bimonthly followed by a re-randomization for the aflibercept group at week 16, to switch in ABP-938 group until week 48, with a FU of 52 weeks [81].

In South Korea, SB15 (Samsung Bioepis Co, Ltd) is currently being compared with innovator aflibercept in an RCT enrolling 446 patients with nAMD. Subjects receive three monthly injections followed by a bimonthly regimen until week 48; at week 32, subjects in the aflibercept group will be re-randomized to receive SB15 or innovator aflibercept. The primary outcome is BCVA change from baseline at week 8 [81].

## 4 Public and Global Health Issues

With expanding indications of antiangiogenic drugs for AMD, as well as with the increasing number of drugs becoming available, drug expenditure in this therapeutic field has grown [93].

In recent years, much of the debate on antiangiogenic drugs for retinal vascular diseases has focused on the use of off-label bevacizumab instead of ranibizumab [94]. The debate on the efficacy and safety of bevacizumab versus ranibizumab for AMD started after CATT (an RCT sponsored by the National Institutes of Health comparing ranibizumab and bevacizumab published in 2011) found a similar efficacy of the two drugs but more SSAEs with bevacizumab [94]. At the time, bevacizumab (off-label) cost $US40 and ranibizumab (approved) cost $US2000. After a few years of discussion and polemics, based both on the sparse available data and on regulatory issues, a Cochrane systematic review [95] of non-industry-sponsored RCTs did not detect a difference between intravitreal bevacizumab and ranibizumab for deaths, all SSAEs, or specific subsets of SSAEs in the first 2 years of treatment, with the exception of gastrointestinal disorders.

Safety related to the sterility of the production chain of off-label bevacizumab was also of great concern in India after counterfeit bevacizumab had caused outbreaks of sterile and infectious post-injection endophthalmitis in several countries, leading to a temporary halt of its authorization for ophthalmic use [96]. A recent study found that in-house compounded injections of bevacizumab can reduce post-injection endophthalmitis to a minimum with maintenance of proper asepsis and strict protocols by the compounding pharmacy [97].

As noted in Sect. 3, biosimilar drugs have been developed to contain drug costs for the treatment of a range of diseases, including retinal vascular conditions. The fact that many of these drugs are produced locally and there is greater flexibility for drug approval makes India and some East Asian countries open to earlier testing of new biosimilar drugs

than the USA and Europe [81]. Cost is an important determinant of medical decision making and drug selection in most countries, and this makes a shift towards less expensive biosimilars an attractive strategy. The VRSI survey established that Indian physicians are well aware of biosimilars and that there is an increasing trend toward prescribing a ranibizumab biosimilar [90]. A third of the respondents felt that Razumab is appropriately priced, but they acknowledged that a further price reduction would be necessary for Razumab to become the drug of first choice. The US patents on Lucentis and Eylea will end in 2020, whereas the European patents expire in 2022 and 2025, respectively. With patents of these biologics about to expire, and the growing acceptance of biosimilars, a shift from branded drugs toward biosimilars in developed nations may occur.

Key issues regarding drug effectiveness with biologics for long-term conditions are the ability to deliver the intravitreal injections in a way that not only minimizes costs but also, and first of all, maximizes benefits. This means that logistics and human resource problems may have the same impact as an ineffective drug on health outcomes. In fact, both undertreatment and noncompliance are common in low- and middle-income countries and in industrialized countries [98, 99]. In age-related conditions, compliance is an issue since the burden of care from multimorbidity and polytherapy is substantial. Despite all these concerns, baseline vision can be maintained on average if patients are followed and injected regularly, as shown in a UK study, which also found that, at 10 years, one-third of eyes had a level of vision that allowed driving (20/40) [100].

Equity issues also affect the appropriateness of the delivery of intravitreal injections, even in industrialized countries. A study conducted in England found wide variation in the provision of anti-VEGF intravitreal injections across services [101]. The occurrence of AMD is in itself related to education, employment, and household income, independently of cardiovascular risk factors [102].

## 5 Conclusions

The effectiveness and safety of intravitreal drugs for AMD is related to not only drug properties but also factors that affect the provision of services in clinical pathways, and the interaction between patients and services is as critical as efficacy and safety when maximizing health outcomes for these patients.

## Declarations

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