Molecular and Clinical Aspects of Anti-VEGF Drugs

Subjects: Ophthalmology

Contributor: Bo-Hyun Moon , Younghwa Kim , Soo-Young Kim

Vascular endothelial growth factor (VEGF) is a major angiogenic molecule that induces choroid neovascularization (CNV). VEGF has five ligand member in human: VEGFA, VEGFB, VEGFC, VEGFD, and placenta growth factor, and there are three receptors: VEGFR1, VEGFR2 and VEGFR3. VEGFs play an important role in vascular development and choroid maintenance in the normal eye. The basolateral secretion of VEGF from the retinal pigment epithelium (RPE) continues throughout life and mediates RPE survival. However, the increase in VEGF secretion from RPE and the loss of RPE polarity are causes of the pathologic CNV condition. Since the off- label bevacizumab started to be used to treat CNV, neovascular age-related macular degeneration (nAMD), there are several anti-VEGF agents approved: pegaptanib, ranibizumab, aflibercept, conbercept, brolucizumab, faricimab.

retina neovascularization choroid retinal pigment epithelium

1. Bevacizumab (Avastin, Genentech)

Bevacizumab was the first anti-VEGF drug approved for the treatment of metastatic colon carcinoma by the US Food and Drug Administration (FDA) in February 2004 and by the European Medicines Agency (EMA) in January 2005. Bevacizumab binds with all isoforms of VEGFA and has been used off-label by medical clinicians for nAMD treatment due to its good efficiency and relatively cheap price. Specifically, in the United States, a single dose of bevacizumab costs approximately 40 times less than a single dose of ranibizumab [1]. However, for ocular use, bevacizumab should be repackaged into small doses under aseptic conditions because the original package is in a 4 mL (100 mg) or 16 mL (400 mg) vial at a concentration of 25 mg/mL. There are several biosimilars of Avastin that have been approved by the FDA and/or EMA [2]: Mvasi (Amgen, September 2017 FDA approved by FDA, January 2018 by EMA), Zirabev (Pfizer, February 2019 by EMA, June 2019 by FDA), Alymsys (Amneal pharmaceuticals, March 2021 by EMA, April 2022 by FDA), Vegzelma (Celltrion, August 2022 by EMA, Sep 2022 by FDA), Aybintio (Samsung bioepis, August 2020, approved by EMA), and Onbevzi (Samsung bioepis, November 2020 by EMA). Additionally, there are other biosimilars such as Avergra (Biocad, Russia), approved by the Russian Ministry of Health, and BAT1706 (Bio-Thera Solutions, China), approved by the China National Medical Products Administration.

2. Pegaptanib (Macugen, Bausch & Lomb)

Pegaptanib (Macugen; Bausch & Lomb, Laval, Canada) was originally developed by Gilead Science and licensed out to Eyetech/Pfizer and then to Bausch & Lomb. Pegaptanib is an oligonucleotide aptamer that specifically binds and inhibits VEGFA165. This now-discontinued drug, pegaptanib, was the first drug to be approved for nAMD treatment by the FDA in December 2004. However, pegaptanib, the specific VEGFA165 blocker, failed in the post-marketing stage due to the more efficient and effective bevacizumab and ranibizumab [3]. The insufficient effectiveness of the VEGFA165 blocker pegaptanib may be attributed to its exclusive inhibition of VEGFA165 and not any other isoforms of VEGFAs. Pegaptanib does not inhibit any other VEGFAs, even including the VEGF165b form, which is constitutionally very similar to the VEGFA165 [4] as mentioned above. In contrast, bevacizumab and ranibizumab are pan-blockers of VEGFAs. These indicate that more isoforms, as opposed to only VEGFA165, are involved in nAMD pathology and that the pathological mechanisms of VEGFs and VEGFRs in nAMD are more complicated than previously considered.

3. Ranibizumab (Lucentis, Genentech)

Ranibizumab is an antigen-binding fragment (Fab) derived from bevacizumab (**Figure 1**), with a higher affinity for VEGFA compared to the parental bevacizumab Fab molecule [5]. It is further considered that the smaller size of the Fab, in contrast to a full antibody format, allows for better diffusion from the vitreous into the outer retina, and quicker clearance from systemic circulation, but with similar local ocular retention. A clinical comparison between ranibizumab (0.5 mg) and bevacizumab (1.25 mg) using the same monthly treatment protocol showed no difference in visual acuity (NCT00593450). It is also speculated that a ranibizumab treatment composed of smaller functional doses may be safer than bevacizumab, especially with the consideration of the data that there are higher rates of serious hospitalized systemic adverse events in bevacizumab-treated patients than those of ranibizumab patients [6]. Fab has no effector domain of antibody and no Fc receptor (FcRN) recycling, which indicates better clearance from the whole body system than full-size antibody drugs, and the functional concentration of Fab is almost half that of full-size antibody in the same molar concentration because Fab has one binding site within it, whereas antibody has two binding sites. Ranibizumab is currently used off-label for the treatment of retinopathy of prematurity (ROP). Byooviz (SB11, ranibizumab-nuna, Samsung Bioepis, South Korea) is the first biosimilar approved by the US FDA (September 2021) to treat nAMD [7]. Ranibizumab-eqrn Cimerli (Coherus Biosciences) is the second approval from the US FDA (August 2022). There are several biosimilars of rabibizumab, such as FYB201/CIMERLI^{TM1} (Formycon AG, German) [8], CKD-710 (Chong Kun Dang Pharmaceutical, South Korea) [9], R TPR 024 (Reliance Life Sciences, India), Xlucane (Xbrane, Sweden), and SJP-0133 (Kidswell Bio/Senju Pharmaceutical, Japan), on the track towards approval [7].

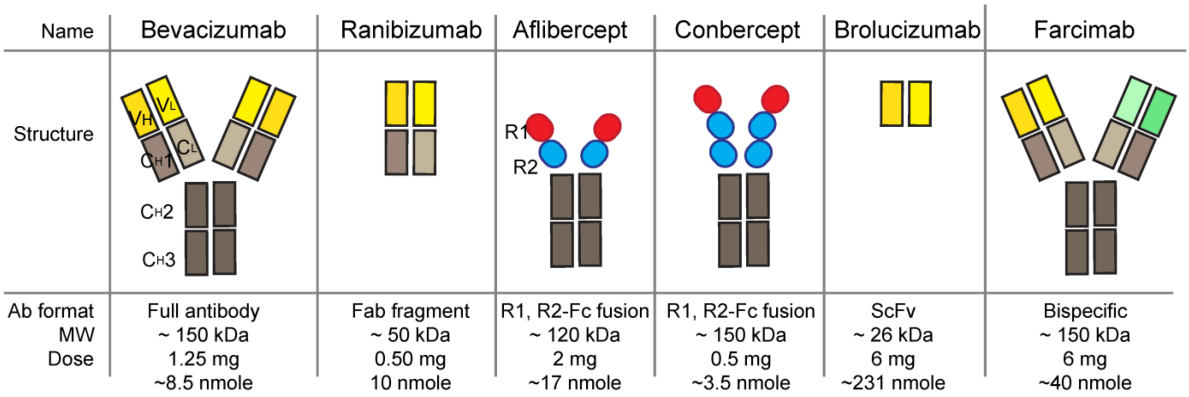

Figure 1. Illustrative structure of anti-VEGF antibody-derived drugs. Molecular weights, clinical doses, and approximate molar amounts of clinical doses are summarized. Region of anti VEGF is indicated by yellow domains and region of anti-ANG2 is indicated by green. V_H, variable region of heavy chain; V_L, variable region of light chain; C_H1, constant region 1 of heavy chain; C_H2, constant region 2 of heavy chain; C_H3, constant region 3 of heavy chain; C_L, constant region of light chain.

4. Aflibercept (Eylea, Regeneron Pharmaceuticals)

Aflibercept is a soluble chimeric recombinant Fc fused protein (FcFP) consisting of VEGFR1 (domain 2), VEGFR2 (domain 3), and the Fc portion of IgG1. This VEGF trap, Eylea (2 mg), was approved in 2011 for the treatment of nAMD with an extended interval of 2 months. A clinical trial comparing the monthly or every-2-month injection of aflibercept (0.5 mg and 2 mg) with the monthly injection of ranibizumab (0.5 mg) showed equivalent efficacy and safety among them [10]. Aflibercept exhibits a higher affinity with VEGFA than bevacizumab or ranibizumab and additionally targets VEGFB and PGF [11]. Aflibercept (0.4 mg) is currently the first anti-VEGF drug to be approved by the FDA (January 2023) for the ROP treatment [12], whereas ranibizumab is for off-label use for the ROP. A real-world meta-analysis between aflibercept and ranibizumab in the ROP treatment could/will provide valuable insights into aspects of efficacy and safety in the near future.

5. Brolucizumab (RTH258, Beovu, Novartis)

Brolucizumab was approved in 2019 for the treatment of nAMD with an extended drug treatment interval of up to 3 months. Brolucizumab is a humanized rabbit anti-VEGF antibody fragment single-chain fragment variable (scFv) in which variable fragment heavy chain (VH) and variable fragment light chain (VL) domains are linked together into one protein, forming an scFv. The small size (~26 kDa) and removed effector fragment crystallizable (Fc) region of brolucizumab are speculated to have greater potential for efficacy and safety due to its high rate of retinal penetration and high rate of clearance in serum (**Figure 1**). This speculation was proven in reality when the brolucizumab serum peak time showed 1–6 h, shorter than other anti-VEGF agents, whereas the ocular retention time was similar [13]. Clinical trials comparing the noninferiority of brolucizumab (6 mg) versus aflibercept (2 mg) showed comparable visual gains and superior anatomical outcomes with similar safety results [14][15][16]. However, in post-marketing surveillance, there were unexpected adverse events on the intraocular inflammatory spectrum,

including retinal vasculitis and retinal vascular occlusion [17]. As a result, a warning and precaution regarding these potential events were added to the US FDA product label in 2020. A continued safety comparison study (NCT03710564) between brolucizumab (6 mg, every 4 weeks of administration) and aflibercept (2 mg, every 4 weeks of administration) revealed a higher risk of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion, with rates of 9.3% vs. 4.5% for brolucizumab and aflibercept, respectively [18]. Patient blood samples experiencing ocular inflammatory adverse events disclosed high titers of anti-brolucizumab antibodies and exhibited robust T cell responses, indicating the immunogenicity of brolucizumab in a certain group of patients [19]. The currently licensed dose of brolucizumab is over 20 times greater than that of ranibizumab in molar concentration [13] (**Figure 1**). In consideration of doses and molar concentrations among other anti-VEGF drugs, using brolucizumab at the same or similar molar concentration may remove the adverse events or reduce the rate.

6. Conbercept (KH902, Lumitin, Chengdu Kanghong Biotechnology)

Conbercept is a soluble decoy/trap, similar to aflibercept, and a recombinant fusion protein of VEGFR1 (domain 2), VEGFR2 (domains 3, 4), and the Fc of IgG1. Compared to aflibercept, conbercept has an additional domain 4 of VEGFR2, which is alleged to enhance affinity and prolong the half-life of the molecule [20]. Conbercept binds to multiple VEGF members such as VEGFA, -B, and PGF as aflibercept does. Conbercept (Kd = 0.5 pM) [21] and aflibercept (Kd = 0.66 pM) [22] have similar binding affinities to VEGFA165 and have similar vitreous half-lives at 4.2 days [23] and 4.79 days [24], respectively, in rabbits. Conbercept was approved for nAMD treatment at extended 3-month interval injections by the China National Medical Products Administration in 2013. In clinical trials conducted in China, conbercept was injected at doses of 0.5 or 2.0 mg every month for 3 months, followed by injections every 3 months for 12 months, and then presented a visual acuity of 9- to 15-letter gains: 14.31 ± 17.07 letters (0.5 mg as necessary), 9.31 ± 10.98 letters (0.5 mg every month), 12.42 ± 16.39 letters (2.0 mg as necessary), and 15.43 ± 14.70 letters (2.0 mg every month) compared to the baseline [20]. So far, more than 0.36 million patients in China have received conbercept treatment, although the published pharmacodynamic data of conbercept in the eyeballs and serums of nAMD patients after treatment are still insufficient. A global phase 3 clinical trial for conbercept (NCT03577899) was projected for its comparison with aflibercept in more than 300 sites across 30 countries in September 2018. However, the global clinical trial was dropped in 2020 due to the COVID-19 pandemic, which resulted in a large number of patients discontinuing their treatment and missing follow-up. There are several reports on meta-analyses of clinical observations of conbercept treatment with different results [25][26], so the properly designed phase 3 clinical data publication about the safety and efficacy of conbercept treatment will be critical and impactful for all those in this sector of the scientific and medical communities.

7. Faricimab (Vabysmo, Genentech)

Faricimab is the most recent drug approved for nAMD treatment by the US FDA in January 2022. Faricimab is a bispecific monoclonal antibody that blocks VEGFA and angiopoietin-2 (ANG2) (**Figure 1**). Faricimab has an inhibitory effect on both VEGFA and ANG2, with extended treatment intervals of up to 3 months. Faricimab has

been shown to be non-inferior to ranibizumab (phase 2) and aflibercept with up to 4-month interval treatment protocols (phase 3) [27][28][29][30]. Faricimab showed a similar rate of serious ocular adverse events to aflibercept and no evidence of occlusive retinal vasculitis [30][31]. ANG2 is one of the pro-angiogenic molecules elevated in the vitreous of patients with retinal vascular diseases [32][33][34]. ANG2 binds to the TIE2 transmembrane receptor tyrosine kinase and competes with ANG1. ANG2 and ANG1 have different functions with the same receptor, TIE2 binding. The binding of ANG2/TIE2 decreases vascular stabilization, whereas ANG1/TIE2 increases vascular stability and inhibits permeability. The coexpression of ANG2 and VEGFA in ischemic retina accelerated neovascularization [35], and the combinatory inhibition of VEGFA and ANG2 more aggressively reduced vessel lesions compared to the single treatment in CNV mice and laser-induced non-human primate models [34]. In addition, the FcRN and FcγRs binding of faricimab is disabled to inhibit Fc-medicated effector function and FcRN recycling, endowing better safety and systemic clearance [34]. Among the anti-VEGF therapeutics so far, faricimab is considered the most effective and safest for nAMD treatment.

8. Ranibizumab Ocular Implant (Susvimo, Genentech)

Susvimo, a port delivery implant with ranibizumab, was approved by the US FDA in October 2021 for the nAMD treatment. Susvimo is a ranibizumab delivery system that consists of a silicon shell containing a drug reservoir that is implanted into the eye through a sclera and pars plana incision and continuously releases ranibizumab over a period of 6 months in the implanted eye [36][37]. The susvimo implant system is non-degradable and is refilled every 24 weeks. At the phase 3 clinical trial, susvimo (every 24 weeks) was non-inferior to ranibizumab injection (0.5 mg every month) in gaining visual acuity within 9 months [38]. However, susvimo prescribing information warns of a threefold higher rate of endophthalmitis than the monthly intravitreal (IVT) injection of ranibizumab, as well as conjunctival erosion and retraction.

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