Review Article

A narrative review on the role of abicipar in age-related macular degeneration

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Abstract: In developed countries, age-related macular degeneration (AMD) is the main cause of visual impairment in the elderly. Though the etiology of AMD is still unclear, it has been well understood that vascular endothelial growth factor (VEGF) is involved in the development of aberrant vasculature that represents the neovascular AMD (nAMD). Hence, VEGF inhibition is a more effective way to control nAMD. Pegaptanib, ranibizumab, and aflibercept are three drugs approved by the US Food and Drug Administration (FDA) to treat nAMD. Bevacizumab (an anti-VEGF medication comparable to ranibizumab) is already widely used off label. Existing anti-VEGF medicines are made up of antibodies or pieces of antibodies. Synthetic designed ankyrin repeat proteins (DARPins) imitate antibodies introduced recently by evolutions in bioengineering technology. These agents are designed to have high specificity and affinity to a specific target, smaller molecular size, and better tissue penetration, making them more stable and longer-acting at less concentration. Abicipar pegol (Allergan, Dublin, Ireland) is a DARPin that interlocks all VEGF-A isoforms. It has a greater affinity for VEGF and a longer intraocular half-life than ranibizumab, making it a feasible anti-VEGF agent. This review describes the properties and efficacy of abicipar, the new anti-VEGF agent, in clinical practice, which aims to improve outcomes, safety, and treatment burden of nAMD.

Keywords: Abicipar pegol; age-related macular degeneration (AMD); choroidal neovascularization (CNV); vascular endothelial growth factor (VEGF)

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Overview

Age-related macular degeneration (AMD) is the main reason for vision impairment in the elderly in industrialized countries (1). AMD affected 196 million individuals worldwide, with a prevalence rate of 8.69% in 2020, and this number is predicted to grow to 288 million by 2040 (2). AMD affects about 11 million individuals in the USA, a prevalence comparable to all invasive malignancies together and even more than double those of Alzheimer's disease. Because of this high incidence, AMD costs the USA $4.6 billion in direct healthcare expenses each year (3). Thus, it demands the attention of all eye care providers.

AMD is a neurodegenerative condition that predominantly influences the macular (central) area of the retina; however, the cause behind this macular tendency is unknown. Different classification and grading systems have been used to classify AMD based on various clinical and paraclinical findings. The Age-Related Eye Disease Study (AREDS) employed a grading system based on standardized

stereoscopic 30-degree color fundus photographs. It showed satisfactory reliability for detecting the onset of advanced AMD in the cohort (4). Classification of Atrophy Meetings (CAM) program suggested an optical coherence tomography (OCT)-based classification for retinal atrophy in AMD. This categorization provides a more comprehensive description of the alterations that occur in AMD than can be seen with only color fundus imaging (5). Traditionally, AMD can be divided into the dry (non-exudative, non-neovascular) type and wet (exudative or neovascular), depending on the presence of excessive neovascularization. The distinction between late AMD, which includes neovascular AMD (nAMD) and an advanced dry form known as geographic atrophy (GA), and early AMD, which consists of all other types, arises from focusing on the severity of visual impairment (6). Although more than 80% of AMD cases are non-neovascular, most impaired vision cases are due to its neovascular type (7). This review highlights abicipar, a novel anti-vascular endothelial growth factor (VEGF) drug designed to improve nAMD management. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/aes-21-45).

Methods

The electronic databases PubMed, Medline, and Scopus were searched for relevant papers. In order to guarantee that the scope of the study was as broad as feasible, all scientific articles published in English between January 1970 and June 2020 were chosen. When an English abstract of a non-English work was available, it was used. Registered trials were also checked https://clinicaltrials.gov, https://www.cochranelibrary.com, and https://who.int. The utilized keywords were including "age-related macular degeneration", "dry age-related macular degeneration", "wet age-related macular degeneration", "Abicipar", "Anti-VEGF therapy", "choroidal neovascularization", "vascular endothelial growth factor", and their combinations.

Dry AMD

Dry AMD is clinically specified by presence of intermediate-size (63 µm or larger) drusen [yellow sub-retinal pigment epithelium (RPE) deposit], RPE pigmentary alterations, and subretinal deposits called reticular pseudodrusen (8). These pigmentary anomalies are the clinical expression of RPE degeneration that can lead to death of the RPE cells and even the overlying photoreceptors. Multiple medium-sized drusen, large-sized drusen, RPE pigmentary alterations, and duration of AMD are all independent risk factors for late AMD (8). Eventually, in late dry AMD or GA, RPE loss plaques fuse and form a large debilitated area. When this condition affects the fovea, vision loss is severe. However, vision loss is usually slow in dry AMD (9). There is no clinically available treatment for dry AMD to slow the expansion or revert vision loss. Therefore, preventive interventions are remarkable to dry AMD (10). AREDS and AREDS 1 indicated that the higher the dietary intake of micronutrients (including minerals, vitamins, and carotenoids), the lower the risk of advanced AMD (11).

nAMD

In nAMD, abnormal neovascularization alters the normal vascular structure of the retina. Choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy (PCV) are common abnormal vascular presentations in nAMD (6). The nAMD is caused by a dynamic complex interplay involving lipofuscinogenesis, drusenogenesis, and inflammation, culminating in neovascularization (12). Local inflammation and perhaps ischemia interrupt a precise interaction between many stimulators and inhibitors, which might contribute to an imbalance in angiogenic and angiostatic factors, resulting in aberrant choroidal angiogenesis (13). If bleeding and serous exudation into the macula are not controlled, fibrosis and scar formation occur, resulting in diminished central vision (14).

Treatment options

Macular photocoagulation has historically been used to restrict the damage caused by choroidal lesions, as seen in nAMD (15). ANCHOR study showed photodynamic therapy (PDT) provided lower clinical benefits than ranibizumab in patients with AMD with new-onset, predominantly classic CNV (16). However, PDT has been employed as a second-line treatment option in nonresponder nAMD patients and an adjuvant treatment to enhance anti-VEGF effects. The results of a case series showed that five of eight nonresponder eyes were treated successfully with a modified PDT protocol following a 36-month follow-up period (17).

In nAMD treatment, photobiomodulation, intravitreal corticosteroid injections, and surgical removal of CNV have all been used (16,18). Some of these modalities are currently

being evaluated; however, due to poor visual results or lack of disease control over a long period as compared to VEGF antagonists, they have a limited role in the treatment of nAMD (16,18).

Anti-VEGF intravitreal agents have been raised as the standard of care in the treatment of nAMD (19). Many clinical trials on VEGF antagonists represent valuable evidence that can assist clinicians in applying these factors with considerable success. Although anti-VEGF therapies have dramatically changed the care of nAMD, this area continues to develop to supply patients with better choices. Numerous in-progress trials focusing on the alternative pathways of retinochoroidal angiogenesis like platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), and epidermal growth factor (EGF) have had remarkable findings and may revalorize current approaches (20,21). First, in cancer biology, Folkman *et al.* studied some pioneering investigations which showed the importance of VEGF in vascular biology (22). VEGF family of proteins includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E, and placental growth factor (PlGF). VEGF-A has a critical role in developing nAMD. These proteins activate the VEGF receptors via a tyrosine kinase-based signaling pathway, subsequently altering endothelial cell proliferation and migration that translate to angiogenesis and increased vascular permeability (23). Thus, targeting the VEGF and VEGF receptors, especially the VEGF-A, has gained an essential role in managing nAMD.

Anti-VEGF therapy

The development of anti-VEGF therapy has revolutionized the treatment of nAMD. Pegaptanib, ranibizumab, bevacizumab, aflibercept, conbercept, brolucizumab, abicipar-pegol, and faricimab are VEGF antagonists used in treatment of the nAMD (24). Pegaptanib (Macugen, Eyetech Pharmaceuticals, USA), a 28-nucleotide RNA aptamer specific for the $VEGF_{165}$ isoform (the prominent VEGF isoform in humans, mainly corresponded to pathological angiogenesis), the US Food and Drug Administration (FDA) approved for nAMD treatment in 2004 (25). VISION trials showed significant continuing visual benefits in patients who received Pegaptinib (26). Afterward, newer VEGF antagonists have been introduced and extensively replaced the use of pegaptanib. In 2006, the FDA approved ranibizumab, a monoclonal antibody fragment against VEGFA, to treat nAMD (16). ANCHOR and MARINA, two key studies, showed the effectiveness and safety of ranibizumab in nAMD (16,27).

Bevacizumab is a monoclonal, humanized, full-length antibody that FDA approved only in the treatment of colorectal cancer, non-small cell lung cancer, cervical cancer, glioblastoma, and renal cell carcinoma (28). As a less expensive anti-VEGF treatment, it has also been used off-label in nAMD (29). IVAN (30), CATT (31), and several other trials, such as MANTA (32), GEFAL (33), and LUCAS (34), have shown the non-inferiority of bevacizumab compared to ranibizumab in the treatment of nAMD.

Aflibercept is a completely human recombinant fusion protein composed of the immunoglobulin binding domain of VEGF receptors 1 and 2 joined to the Fc region of IgG. It binds to all VEGF-A isoforms, VEGF-B, and PlGF (35). Aflibercept is one of Regeneron's unique Trap product family, which catches, holds, and blocks specific cytokines (36). Aflibercept was approved by the FDA for the treatment of nAMD in 2011 (37). Conbercept (Chengdu Kanghong Biotech Company, Sichuan, China) is another medication of the VEGF Trap family made up of a 143 kDa human DNA sequence with a profile similar to that of aflibercept (38). The major difference is the addition of a VEGFR2-specific component, which was intended to improve conbercept's potency and durability in producing a higher affinity for VEGF-C (39). In China, the phase 3 PHOENIX study has had acceptable outcomes, and the drug was approved (38). PANDA-1 and PANDA-2 are phase 3, randomized, quadruple-masked, multi-centered trials that assess three arms: 0.5 mg conbercept, 1.0 mg conbercept, and 2.0 mg aflibercept. The study's primary objective is the mean change in best-corrected visual acuity (BCVA) after 36 weeks. The results of this study are expected to be available by the end of 2021 (40,41). Brolucizumab, a humanized single-chain antibody fragment, is the last VEGF antagonist which has gotten FDA approval in the treatment of nAMD (42). The approval was based on results from the HAWK and HARRIER trials, which showed that Brolucizumab was non-inferior to aflibercept in terms of mean improvement in visual acuity at 1 year, and with a presumably lower injection schedule (43). Faricimab is another anti-VEGF agent. In addition to targeting VEGF-A, faricimab also targets the Ang-Tie/pathway, making it a potentially beneficial bispecific medication. Phase II STAIRWAY and AVENUE trials demonstrated clinical effectiveness in the treatment of w-AMD, while the phase II BOULEVARD trial demonstrated superiority to monthly ranibizumab in the management of diabetic macular edema (DME) when

administered on a monthly basis (as opposed to every 3 months). Faricimab is now pending FDA approval to treat nAMD and DME (44).

Abicipar

Abicipar pegol (Allergan, Dublin, Ireland) is a novel anti-VEGF agent belonging to the designed ankyrin repeat proteins (DARPin) family. This family has composed of four to six repeated motifs of natural ankyrin proteins that can attach to a specific target with a high affinity in the picomolar range (45). Aside from their excellent affinity and selectivity, DARPin molecules are highly stable, as evidenced by melting temperatures that are frequently above 80 ℃, and even in some instances over 100 ℃ (46). A regular four- or five-repeat DARPin structure has a molecular mass of 14 to 18 kDa, or one-tenth the mass of an antibody or one-third the weight of a Fab fragment (47). These characteristics lead to lower drug concentration required to achieve appropriate tissue concentration and biological effects of the DARPin family to treat different pathologies like neoplasia (48).

Abicipar, formerly known as MP0112 and AGN-150998, is a 135-amino-acid protein with an estimated molecular weight of 14 kDa (49). It contains two DARPin monomers unique to human VEGF-A, as well as bordering N-capping and C-capping motifs. This protein, when is coupled to a 20-kDa polyethylene glycol (PEG) component, forms abicipar pegol (50). Abicipar has a high binding affinity for human VEGF-A_{165} of 486 fM, which is 100 times higher than ranibizumab and bevacizumab. This is also higher than the affinity of aflibercept for $VEGF_{165}$ (200 fM) (47). Abicipar can also bind to human VEGF-A_{110}, rabbit, and rat VEGF-A_{165}, and it can cross-react with VEGF-A of other species to aid preclinical medication progression (47). Abicipar has a greater and longer intraocular half-life than ranibizumab, making it a potentially longer-lasting anti-VEGF treatment with fewer injections (47). Abicipar reduced angiogenesis in a three-dimensional *in vitro* analysis of VEGF-mediated tube formation with an IC_{50} value of 1.1 nM in a level-based manner (47). In a mouse model of corneal neovascularization, abicipar at a dose range of 8 mg/kg/day for 9 days reduced neovascularization by 84% as compared to the sham treatment. In addition, mice were given 8 mg/kg intraperitoneal abicipar daily for 11 days in the prevention mode (day 1 to day 9) or 10 days in the intervention model (day 14 to day 23); in both modes, abicipar suppressed vascular growth (47). In other animal models of retinal neovascularization, abicipar decreased retinal vasculature tortuosity, vasodilation, and leak (47). These *in vitro* and *in vivo* findings advocated the trial of abicipar as a new therapeutic for retinal diseases specified by neovascularization and vascular leakage like nAMD.

Abicipar and AMD

The first Phase I/II trial for abicipar safety, preliminary efficacy in nAMD was an open-label, single ascending dosage study in 32 patients with nAMD to assess the safety, preliminary effectiveness, and pharmacokinetics profile (51). A single intravitreal injection of abicipar in the following dosages was given to each participant: 0.04, 0.1 mg, 0.4, 1, 2, and 3.6 mg. The duration of the follow-up was 16 weeks. Due to one incident of sterile inflammatory endophthalmitis in the 2.0 mg dosage, the maximum tolerated dose was established to be 1.0 mg. For the first 4 weeks after injection, visual acuity ratings were constant or improved relative to baseline; retinal thickness and fluorescein angiography leakage were both reduced in a dose-dependent manner (51). Two other phase I/II trial was carried out in patients with nAMD. One of them completed in 2017 was an open-label study in which group 1 was treated with 3 intravitreal injections of 2 mg abicipar, 4 weeks apart (day 1, weeks 4, and 8). Group 2 received only one 2 mg injection (52). PINE study was another open-label phase I/II study carried out in Japan on 11 nAMD patients. The same outcomes of the previous studies were assessed after a single intravitreal injection of 2 mg abicipar (53).

The REACH was a phase II study that evaluated abicipar 1 mg, abicipar 2 mg, and ranibizumab in subjects with naive nAMD in a multicenter randomized controlled trial. The research comprised a total of 64 patients who were monitored for 20 weeks, with abicipar patients receiving three monthly injections and ranibizumab patients receiving five monthly injections. At week 20, the BCVA change from baseline for abicipar 1 mg, abicipar 2 mg, and ranibizumab was +8.2, +10.0, and +5.3, respectively. At week 20, abicipar 1 mg, abicipar 2 mg, and ranibizumab reduced mean central retinal thickness (CRT) by 116, 103, and 138 μm, respectively. Overall, the improvements in BCVA and CRT in both abicipar groups were similar to those seen with ranibizumab, and they lasted for 3 months after the third abicipar injection. No serious adverse effects were reported (54). Only the findings of 64 individuals of a greater phase-III trial (55) with a total of 271 subjects were presented in this article. BAMBOO in Japan and CYPRESS

in the US are phase-II, randomized, double-blinded, 20-week clinical trials which evaluated comparability of abicipar pegol effects in patients with treatment-naïve nAMD in Japan and the USA. Three monthly intravitreal injections of abicipar 1 or 2 mg or five monthly intravitreal injections of ranibizumab 0.5 mg were given to patients (n=25 in each trial). Three abicipar-treated individuals developed uveitis or vitritis (56). The SEQUOIA and CEDAR are two randomized, multicenter, double-masked, parallel-group, active-controlled, phase 3 clinical trials with identical protocols (57). These trials enrolled subjects with active CNV secondary to AMD. In a pooled analysis based on both trials data, patients (n=1,888) were randomly assigned to 1 of 3 groups: (I) abicipar 2 mg every 8 weeks after three first doses at baseline, weeks 4 and 8; (II) abicipar 2 mg every 12 weeks after three initial doses at baseline, weeks 4 and 12, and (III) ranibizumab 0.5 mg every 4 weeks. The proportion of patients with stable vision at week 52 was 93.2%, 91.3%, and 95.8% in the first, second, and third groups, respectively (57). In SEQUOIA, the proportion of patients who gained more than 15 letters of VA was equal across the abicipar and ranibizumab groups but greater in the ranibizumab group in CEDAR (58). Because of the development of intraocular inflammation, the incidence of drug-related ocular adverse events was greater in groups 1 (16.8%) and 2 (20.4%) than in group 3 (4.5%). The most frequent idiopathic orbital inflammation (IOI) was uveitis and retinitis. This pooled analysis showed abicipar had a higher risk of IOI and endophthalmitis compared to ranibizumab. Aside from endophthalmitis and IOI, no other safety issues were noted (57). MAPLE, a phase-II trial (59) was performed to explore this issue and determined that impurities from the manufacturing process, rather than the active component itself causing IOI. The safety and efficacy of abicipar in the nAMD and adverse events of abicipar in clinical trials are summarized in *Tables 1*,*2*, respectively.

Table 1 Clinical studies that evaluated the safety and efficacy of abicipar in the neovascular AMD

Study	Phase	Baseline age (years)	Patients (N)	Treatment regimen	Follow-up (week)	Letter gain	CRT change (μm)
MP0112 (51)	I/II	78.3±5.3	32	Abicipar 1 mg	4	94%	–95
				Abicipar 2 mg	4	97%	–111
REACH (54)	II	76±10	25	Abicipar 1 mg	20	+8.2	–116
			23	Abicipar 2 mg	20	+10.0	–103
			16	Ranibizumab 0.5 mg	20	+5.3	–138
BAMBOO (56)	II	74.3±7.1	10	Abicipar 1 mg	16	+7.8	–187.3
			10	Abicipar 2 mg	16	+8.9	–196.5
			5	Ranibizumab 0.5 mg	16	+17.4	–230.4
CYPRESS (56)	II	83.4±7.8	10	Abicipar 1 mg	16	+4.4	–106.5
			10	Abicipar 2 mg	16	+10.1	–112.8
			5	Ranibizumab 0.5 mg	16	+15.2	–124.4
MAPLE (59)	II	78.3±8.21	124	Abicipar 2 mg	28	+3.6	–82.5
SEQUOIA (57)	III	76.0±8.4	949	Abicipar 2 mg[a]	52	+8.3	–146.8
				Abicipar 2 mg[b]	52	+7.3	–141.7
				Ranibizumab 0.5 mg	52	+8.3	–147.1
CEDAR (57)	III	76.5±8.3	939	Abicipar 2 mg[a]	52	+6.7	–141.5
				Abicipar 2 mg[b]	52	+5.6	–150.1
				Ranibizumab 0.5 mg	52	+8.5	–141.3

[a], abicipar pegol 2 mg on day 1, week 4, week 8 and every 8 weeks after that through week 96; [b], abicipar pegol 2 mg on day 1, week 4, week 12 and every 12 weeks after that through week 96. AMD, age-related macular degeneration.

Table 2 Some adverse events of abicipar in clinical trials

Study	Adverse events (AEs)
MP0112 (51)	AEs were reported in 13 of 32 (41%) patients and included anterior chamber inflammation (5/13 patients); vitritis (4/13 patients); anterior chamber cell flare (3/13 patients); and endophthalmitis (1/13)
	Ocular inflammation resolved without consequence in all eyes; in 36% (4/11), this occurred without treatment, and all others received local anti-inflammatory medication (betamethasone, dexamethasone, tropicamide, or dexamethasone-tobramycin)
REACH (54)	The overall incidence of AEs was 15/25 in the abicipar 1-mg arm, 10/23 in the abicipar 2-mg arm, and 9/16 in the ranibizumab 0.5-mg arm
	Most events were mild or moderate in severity
	The most common ocular AEs (reported in ≥2 patients in any treatment arm) were vitreous floaters, vitreous detachment, retinal hemorrhage, eye pain, conjunctival hemorrhage, and macular scar
	No deaths or other serious AEs were reported in any treatment arm
BAMBOO (56)	Uveitis or vitritis was reported in 2 of 20 abicipar-treated patients. None of the AEs of intraocular inflammation were associated with a sustained loss of vision
	There were no Antiplatelet Trialists' Collaboration (APTC) arterial thromboembolic events reported in the abicipar treatment arms
CYPRESS (56)	Uveitis or vitritis was reported in 1 of 20 abicipar-treated patients that were not associated with a sustained loss of vision
	There were no Antiplatelet Trialists' Collaboration (APTC) arterial thromboembolic events reported in the abicipar treatment arms
MAPLE (59)	Iritis 1/123 (0.81%), retinal haemorrhage 1/123 (0.81%), vitreous haemorrhage 1/123 (0.81%), vitritis 1/123 (0.81%)
SEQUOIA and CEDAR (57)	The incidence of study drug-related ocular AEs was higher in the abicipar Q8[a] (16.8%) and abicipar Q12[b] (20.4%) groups than in the ranibizumab group (4.5%) because of the occurrence of IOI
	Intraocular inflammation AEs in the study eye were reported for 96 patients (15.4%) in the abicipar Q8 group, 96 patients (15.3%) in the abicipar Q12 group, and 2 patients 0.3% in the ranibizumab group
	Uveitis and vitritis were the most common IOI AEs and the onset of IOI was typically early
	The IOI was resolved without sequelae in 74.5%, with sequelae (primarily vision loss) 10.9%, be resolving in 4.2%, and be ongoing in 10.5%
	Retinal vasculitis occurred in 22 (1.8%) abicipar-treated
	Endophthalmitis was reported 1.3% in the abicipar Q8 group, 1.3% in the abicipar Q12 group, and 0.2% in the ranibizumab group
	Ocular AEs other than IOI and endophthalmitis were comparable among treatment groups

[a], abicipar pegol 2 mg on day 1, week 4, week 8 and every 8 weeks after that through week 96; [b], abicipar pegol 2 mg on day 1, week 4, week 12 and every 12 weeks after that through week 96. IOI, idiopathic orbital inflammation.

Conclusions

By developing anti-VEGF therapy, significant progress has been made in the treatment of nAMD and the accompanying visual results and prognosis. Despite this, there are still challenges related to anti-VEGF therapy, and numerous novel therapies are being developed to fix these issues. Abicipar, a DARPin agent, targets VEGF-A isoforms and is being introduced as an alternative for anti-VEGF factors such as bevacizumab, ranibizumab, and aflibercept.

Preclinically and clinically, abicipar offers many potential therapeutic advantages compared to available antibodies, such as high affinity, stability, and small molecular size, and long intervals between injections. Phase III clinical

trials showed abicipar could effectively block VEGF in most patients with 3-monthly intervals between injections. However, abicipar in clinical studies was shown to cause intraocular inflammation in a higher range than ranibizumab requiring more safety assessments.

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