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Review

Avacincaptad pegol, the second approved aptamer medicine – A mini review

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Abstract

Therapeutic oligonucleotides are employed in the treatment of a variety of diseases, primarily functioning through mechanisms associated with gene-silencing technologies. In contrast, aptamers exhibit mechanisms of action that are more akin to those of protein-based monoclonal antibodies. However, owing to their oligonucleotide structure, aptamers possess several advantages over antibodies. Despite these benefits, the adoption of aptamers in clinical medicine has not reached the levels observed with monoclonal antibodies or gene-silencing oligonucleotides. Almost two decades after the approval of pegaptanib, the first approved aptameric therapeutic for the treatment of neovascular AMD (age-related macular degeneration), a second aptamer has recently received approval to treat geographic atrophy (GA), an advanced form of dry AMD. In this review, we aim to provide an overview of the pharmacology and chemistry of avacincaptad pegol, the second approved aptameric drug.

1. Introduction

The term aptamer is derived from the word *aptus* (Latin, “to fit”) and *meros* (Greek, “place”). Aptamers are short oligonucleotides that are able to bind to specific molecular targets in a manner similar to antibodies. Due to this, aptamers are often referred to as “chemical antibodies”[1,2]. Aptamers, however, have several advantages over the protein-based antibodies. Their synthesis is cheaper and easier to standardize. They can bind to a wider range of target molecules (since the target does not need to be immunogenic). Additionally, aptamers exhibit relatively low immunogenicity and greater thermal and chemical stability[2]. However, a significant drawback is their relatively low metabolic stability. which can be overcome by synthetic modifications. These modifications must be compatible with the applied synthetic and development method (for example, polymerases must be able to accept them as building blocks),

cost-effective, and should not interfere with the ability to bind to the target. Most common modifications include replacing the 2'-hydroxyl group of the ribofuranose ring with an amino group (NH_2), a fluorine atom (F), or a methoxy group (OMe). Another prevalent modification is "capping" the 3' end of the oligonucleotide chain. In this case, a thymidine residue is linked to the oligomer via a 3'-3' phosphodiester bond instead of the normal 5'-3' bond. These modifications increase the resistance of the molecule to nucleases. To reduce renal clearance, cholesterol or polyethylene glycol (PEG) can be attached to the 5' terminus, through tetraethyleneglycol or aminoalkyl linker (usually using a carbamate group to attach them to the aptamer), further improving the half-life time of the aptamer[3,4]. These modifications are depicted in **Figure 1**, and their functions are summarized in **Table 1**.

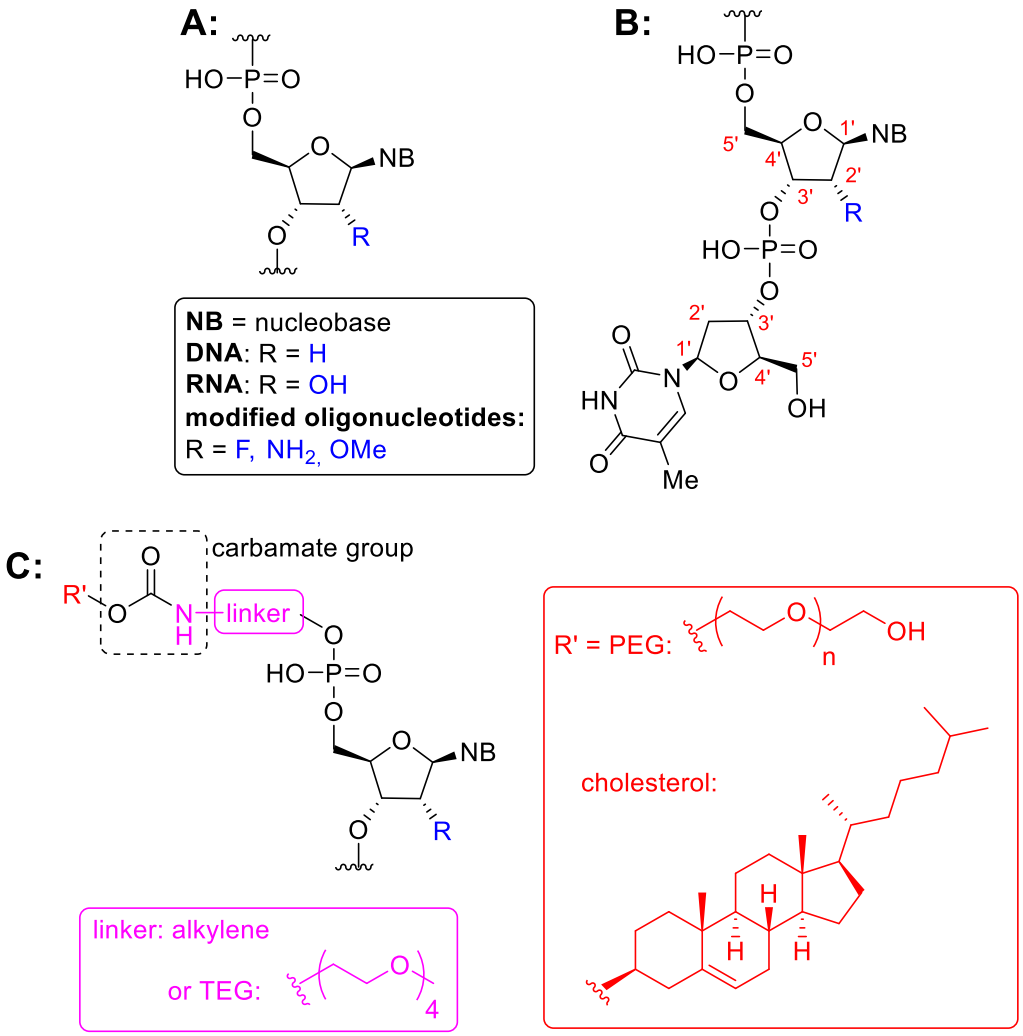

Figure 1. The most common 2'-modifications in aptamers (**A**), 3' cap structure (**B**), and the most common 5'-modifications (**C**)

Table 1. **Key c**hemical modifications of aptamers

Modifications	Advantages	Disadvantages
2'-Fluoro	increased nuclease resistance and target binding	More expensive than 2'-methoxy
2'-Methoxy	cheap increased nuclease resistance	decreased binding affinity
2'-Amino	increased nuclease resistance	increased cost decreased binding affinity
3'-Cap	resistance against 3'-exonucleases	Requires incorporation after synthesis
5'-PEGylation	reduction of renal clearance	Requires incorporation after synthesis
5'-Cholesterol conjugation	reduction of renal clearance	Requires incorporation after synthesis

Age-related macular degeneration (AMD) is a leading cause of blindness in the developed world. Its "wet" (neovascular) form is hallmarked by abnormal choroidal neovascularization (CNV), causing leaking, hemorrhage, and retinal pigment epithelium (RPE) detachment. Vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of wet AMD[5,6]. The first approved aptamer medicine, pegaptanib (Macugen™) targets the 165 isoform of VEGF and was approved in 2004 by the FDA for the treatment of neovascular AMD[7,8]. The "dry" form of AMD is rather characterized by deposit accumulation on RPE and Bruch's membrane (BrM) thickening. An advanced form of dry AMD is geographic atrophy (GA), which is defined by the irreversible loss of RPE, photoreceptors, and choriocapillaris, causing irreversible central vision loss[9]. The overactivation of the complement system is a key factor in the progression of GA[10]. Considering the irreversible nature of the damage caused by GA, current therapies aim to slow down or halt the progression of the disease. In the case of FDA-approved anticomplement therapies, the main endpoint of the clinical trials was the reduction of GA expansion[11].

Avacincaptad pegol is an aptamer that specifically binds to and inhibits complement C5. In 2023, it was approved by the FDA for the treatment of GA secondary to AMD[12]. With this, avacincaptad pegol became the second aptamer medicine to receive approval, following the 2004 approval of pegaptanib[13]. This review aims to summarize the available data on avacincaptad pegol, focusing on pharmacologically relevant information.

2. Chemistry

Avacincaptad pegol is a 39-nucleotide-long PEGylated RNA aptamer[13]. It is formulated in a phosphate-buffered solution. The sequence from 5'→3' terminus is: CGC C**G**C GGU CUC AGG C**G**C UGA GUC UGA GUU U**A**C CUG CG. To enhance nuclease resistance, pyrimidine nucleosides are modified by carrying 2' fluorine atoms instead of the OH, while purine nucleosides are substituted with 2'-OMe groups, except for the 5th G, 17th G, and 32nd A, which are unmodified residues (highlighted in **bold** in the sequence). At the 3'-end, an inverted 3'-3' thymidine cap is coupled, providing additional protection against 3'-exonucleases. At the 5' end, through a hexylamino carbamate linker, a branched polyethylene glycol monomethyl ether (weighing approximately 43 kDa) is attached to the molecule to further extend the half-life time by slowing its clearance[14] (**Figure 2**).

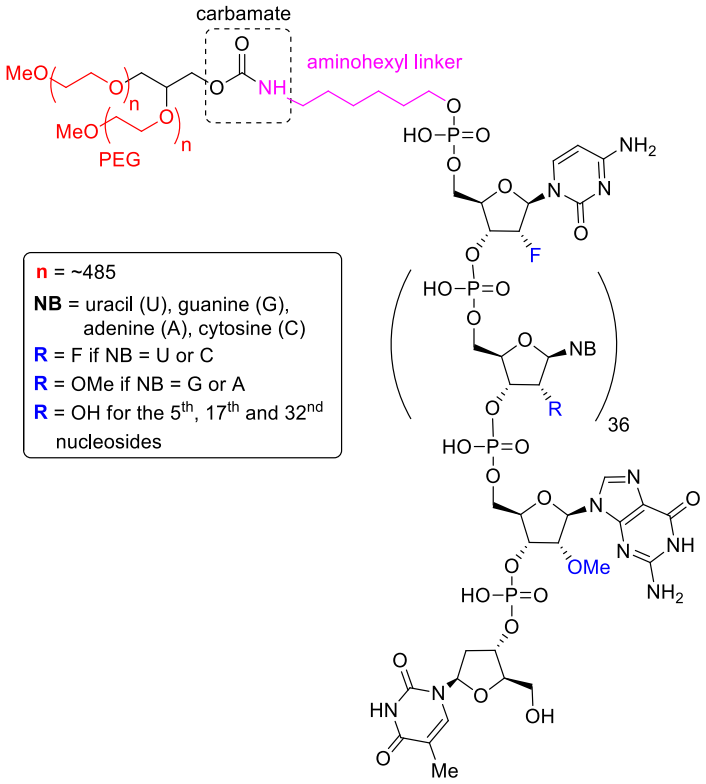

Figure 2. Chemical structure of avacincaptad pegol

3. Mechanism of action

With aging, intrinsic and extrinsic stressors cause accumulating damage to the RPE, leading to the formation of drusen and lipofuscin deposits. Oxidative stress products and deposit components cause inflammation via different pathways, one of which is the activation of the complement cascade. The complement cascade is a part of the innate immune system, consisting of more than 30 proteins. The cascade can be activated in 3 different ways, converging into the cleavage of the C3 protein into C3a and C3b fragments. C3a initiates inflammation, while C3b, together with other complement cleavage products, forms C5 convertase complexes, cleaving the C5 protein into C5a and C5b fragments. C5b, together with C6, C7, C8, and C9, forms the membrane attack complex (MAC), which creates pores on the cell surface, causing the death of the cell (physiologically, the pathogen cells). Host cells express regulatory proteins on their surface, inhibiting the conversion of C3 into C3a and C3b. In AMD, however, the dysfunction of the complement cascade is observed, which probably plays a significant role in the pathophysiology of GA[15].

The normal functioning of the complement system plays an important role not only in the defense against pathogens but also in the maintenance of healthy tissues by facilitating the clearance of apoptotic cells. C3a and C5a signaling is important in maintaining retinal structure and function. Therefore, C5 is a more favorable target for pharmacotherapy since it takes place downstream in the signaling way. This allows the inhibition of C5 activity while preserving C3 activity[9,15].

Avacincaptad pegol selectively binds to the protein C5 and inhibits it, hindering its cleavage into C5a and C5b[14]. Thus, prevents the formation of MAC, reducing cell death and slowing down retinal degradation[12] (**Figure 3**).

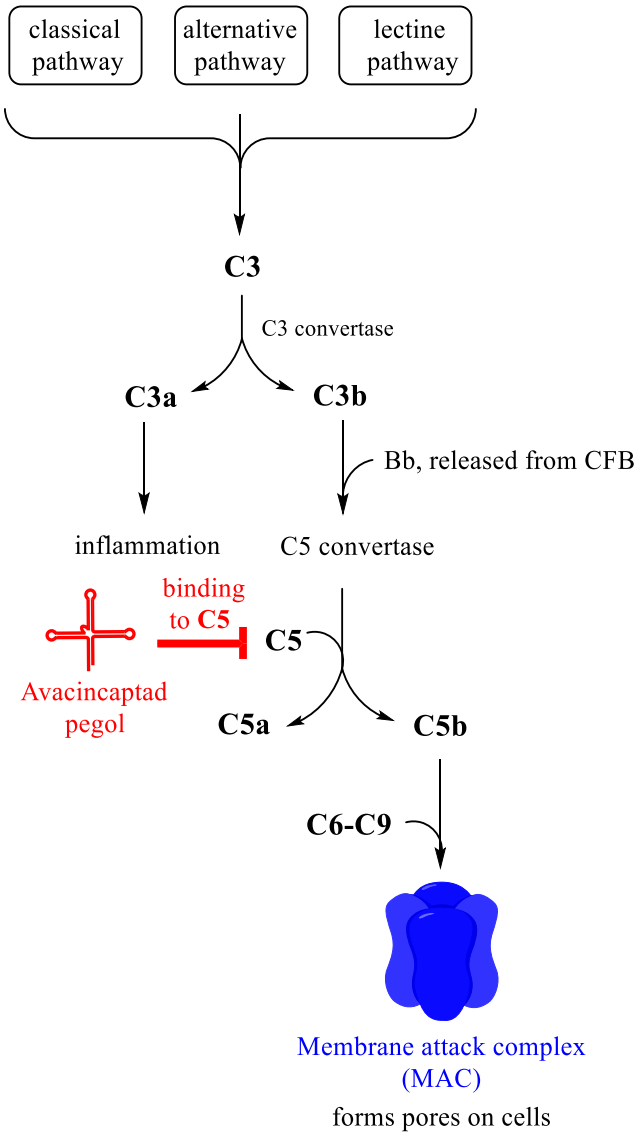

Figure 3. Mechanism of action of avacincaptad pegol, CFB = complement factor B

4. Development and nonclinical results

The common method for the development of aptamers is the systematic evolution of ligands by exponential enrichment (SELEX). It is a cyclic procedure, starting from a pool of random oligonucleotide sequences. These oligonucleotides are incubated with the target molecule, and the ones that bind to it are separated from the rest. By repeating these cycles several times, the oligomers with the highest affinity are selected for further modifications. These chemical modifications may include the incorporation of 2'-OMe groups, conjugation with other molecules, and truncation of the aptamer to shorten it to the minimal effective size. Truncation not only reduces the cost of synthesis but also minimizes the likelihood of undesirable interactions with non-target molecules[16].

Due to the low binding of C5 to random RNA, the SELEX started from a 2’-fluoro-RNA pool, with relatively high RNA and protein concentration. After that, RNA and protein concentrations were gradually reduced in each subsequent round of SELEX. In some experiments, a small amount of trypsin was also added to the incubation to achieve a limited cleavage of the protein into a C5a-like form, as the main target of the aptamer was the C5a-C5b cleavage site. After 12 SELEX cycles, C5-binding aptamers were cloned and sequenced. Hemolytic assays were performed, and C5a release in aptamer-containing serum was determined. Based on the results, the C5C6-coded aptamer was chosen for truncation, resulting in a shortened 38-mer for biased SELEX, which further improved affinity. After round 12, the YL-13 aptamer showed a 10-fold increase (compared to C5C6) in C5 affinity. To investigate which positions could accommodate 2'-OMe substitutions, this modification was integrated into various units. It was revealed that the G5, G17, and A32 positions must contain free 2’-OH groups. These positions take place in the bulges and the loop in the tertiary structure of the aptamer, suggesting that these regions play a significant role in the binding to the target protein. The modified aptamer was able to inhibit hemolysis by human serum in a concentration-dependent manner[17].

In an animal model, intravitreal avacincaptad pegol was able to decrease NaI-induced GA in *Macaca fascicularis* compared to sham. The change in GA area from baseline was one-third less in the avacincaptad pegol group than in the vehicle-treated group. However, the treatment did not affect or alter macular thinning[18].

5. Clinical results

5.1. Efficacy

The efficacy of avacincaptad pegol has been evaluated in two phase III randomized, double-masked, sham-controlled studies, namely GATHER1 (NC T02686658) and GATHER2 (NC T04435366), which demonstrated a significant growth reduction in GA. The pivotal clinical trial GATHER1 involved a total of 286 subjects diagnosed with GA and was conducted in two parallel parts, in which both parts received monthly injections for up to 18 months. In part 1, eyes were randomized in a 1:1:1 ratio to receive either avacincaptad pegol 1 mg (n = 26), avacincaptad pegol 2 mg (n = 25), or sham treatment (n = 26). In phase two, subjects were randomized in a 1:2:2 ratio to receive avacincaptad pegol 2 mg (one 100 µl injection + one sham administration, n = 42), avacincaptad pegol 4 mg (two injections of 2 mg, resulting in a total volume of 200 µl,

n = 83), or sham treatments (two sham administrations, n = 84). Prespecified statistical analyses were designed to compare the outcomes of patients who received 2 mg and 4 mg of avacincaptad pegol and their corresponding sham cohorts. Consequently, the results for individuals administered 1 mg of avacincaptad pegol were not presented[9,19]. Following 12 months of treatment, the primary endpoint — mean change in GA area (square root transformed), as measured by fundus autofluorescence (FAF) at baseline, month 6, and month 12 — demonstrated an absolute difference of 0.110 mm (95% CI: 0.030-0.190; p = 0.0072) in the 2 mg avacincaptad pegol-treated group (a 27.4% reduction), and 0.124 mm (95% CI: 0.038–0.209; p = 0.0051) in the 4 mg recipients (a 27.8% reduction), compared with their corresponding sham cohorts[19].

Avacincaptad pegol at doses of 2 mg and 4 mg did not affect the mean change in best-corrected visual acuity (BCVA) or low luminance BCVA (LL-BCVA) from baseline to month 12 compared to their respective sham groups. The mean changes in BCVA and LL-BCVA were -7.9 and -1.0 letters, respectively, in the 2 mg avacincaptad pegol-receiving cohort (vs. -9.3 and -1.4 letters in its sham cohort), and -3.8 and 1.5 letters, respectively, in the 4 mg treated group (vs. -3.5 and 3.0 letters in the sham cohort)[19].

An updated analysis conducted after 18 months of treatment showed sustained effects, recording a reduction of 28.1% (−0.168 mm) in the 2 mg treatment group (n = 41) and a reduction of 30.0% (−0.167 mm) in the 4 mg treatment group (n = 4), compared to their respective sham recipient groups (n = 78 and n = 64, respectively)[9]. The mean changes in BCVA and LL-BCVA were -12.7 and -2.72 letters, respectively, in the 2 mg avacincaptad pegol-receiving cohort (vs. -15.1 and -3.10 letters in its sham cohort), and -4.27 and 2.85 letters, respectively, in the 4 mg treated group (vs. -7.07 and 1.68 letters in the sham cohort)[9].

The eligibility criteria for participation included individuals who are 50 years of age or older, have a BCVA ranging from 20/25 to 20/320, and present with GA to AMD, which is non-foveal centered and located within 1500 µm from the foveal center. The total area of GA must be between 2.5 and 17.5 mm² (1 to 7 disc areas, as determined through comprehensive screening using FAF imaging captured entirely within field 2). In cases where participants exhibit multifocal GA lesions, at least one of the focal lesions must have an area ≥ 1.25 mm² (0.5 disc areas). The exclusion criteria for this study included GA not secondary to AMD in either eye, any previous treatment for dry or wet AMD (with the exception of oral supplements containing vitamins and minerals),

prior intravitreal treatment for any condition in either eye, and the occurrence of choroidal neovascularization in either eye[19].

The inclusion and exclusion criteria for GATHER2 were similar to those established in GATHER1. In this study, eligible patients were randomly assigned to receive either intravitreal avacincaptad pegol at a dose of 2 mg (n = 225) or a sham treatment (n = 222) once a month for 12 months. After this period, patients receiving avacincaptad pegol were re-randomized to continue with the same treatment either once a month or once every two months, with sham treatment administered in between, for an additional 12 months[20]. The study successfully fulfilled its prespecified primary objective by demonstrating a significant reduction in the mean rate of growth in the GA area. The analysis revealed a difference of 0.056 mm from baseline to month 12 of treatment (95% CI 0.016–0.096; p = 0.0064), recording a 14.3% reduction in the growth rate compared to the sham treatment. Furthermore, the prespecified subgroup analyses indicated that avacincaptad pegol exhibited greater overall effectiveness than the sham treatment in reducing GA growth. However, this efficacy was not observed in certain subgroups: GA ≥ 4 disc areas, visual acuity < 50 letters, none/focal FAF patterns, individuals aged < 75 years, and male participants[20].

A *post hoc* analysis evaluated vision loss within these GATHER trials to quantify the observed treatment effect. The study populations were combined, ensuring that baseline characteristics were balanced across the cohorts: the avacincaptad pegol 2 mg treatment group (n = 292) and the sham group (n = 332). In the assessment of categorical changes in BCVA at the 12-month mark, a lower proportion of patients receiving avacincaptad pegol 2 mg exhibited letter losses of ≥10, ≥15, or ≥20 letters from baseline compared to the sham group. Specifically, 4.0% of the individuals in the avacincaptad pegol 2 mg cohort experienced losses of ≥15 letters, compared to 7.6% of participants in the sham cohort at month 12. Significant separation between the treatment and sham groups concerning losses of ≥15 letters was observed starting from month 9. Furthermore, a time-to-event analysis regarding persistent vision loss classified as a loss of ≥15 BCVA letters over the 12-month period was conducted. The findings revealed a 56% reduction in the relative risk of persistent vision loss of ≥15 BCVA letters (hazard ratio: 0.44; 95% CI: 0.21–0.92) over 12 months[21].

5.2. Safety

In the preliminary phases of clinical studies, the safety and tolerability of avacincaptad pegol were assessed in combination with ranibizumab among subjects diagnosed with

subfoveal CNV secondary to AMD, and were further evaluated in treatment-naive patients with nAMD. The findings indicated that the concomitant administration of avacincaptad pegol alongside the anti-VEGF antibody was well-tolerated, and the majority of reported adverse events were linked to the injection procedure (**Table 2**)[22, 23, 24].

The open-label, parallel-assigned phase I/II clinical trial (NCT 00950638) was the first to evaluate the safety and tolerability of avacincaptad pegol in patients diagnosed with GA[25]. Avacincaptad pegol was administered intravitreally at weeks 0,4 and 8, with additional injections provided at weeks 24 and 36. Safety follow-up procedures after 16 and 48 weeks indicated that avacincaptad pegol is well tolerated with no associated adverse events[26].

The Phase III GATHER1 and GATHER2 pivotal trials further established a consistent and acceptable safety profile (**Table 2**). Most subjects in the treatment and sham cohorts experienced TEAEs, which were higher in the treatment groups (GATHER1 (12 months): 52.2% (2 mg) and 68.7% (4 mg) vs. 34.5% (sham); GATHER1 (18 months): 58.2% (2 mg) and 73.5% (4 mg) vs. 40.5% (sham); GATHER2: 48.9% (2 mg) vs. 37.4% (sham))[19,20]. The most common (≥ 4% of patients in both GATHER1 and GATHER2) ocular TEAEs in the study eye were conjunctival hemorrhage, increased intraocular pressure (IOP), choroidal neovascularization, conjunctival hyperaemia, punctate keratitis, and eye pain. The increase in the IOP observed was associated with the injection procedure. Most events were transient, and the mean IOP returned to near baseline levels at the next follow-up visit[19,20]. Systemic TEAEs were also reported, with the most common being urinary tract infection, nasopharyngitis, falls, and atrial fibrillation[19].

In GATHER1, no patients discontinued treatment due to an AE, and no cases of endophthalmitis or intraocular inflammation were seen in any patient[19]. In the updated analysis after 18 months, one patient of each treatment group experienced a serious AE in the study eye[9]. No ocular or systemic AEs, including serious ones, were deemed treatment-related[9,19].

Unlike GATHER1, serious ocular TEAEs — choroidal neovascularization (0.9% vs. 0.5% (sham)) and reduced visual acuity (0.5% of the sham cohort) — were reported in GATHER2, out of which two (0.9%) in the avacincaptad pegol group and none in the sham group led to study drug discontinuation[20].

One of the most noteworthy AEs reported in the GATHER trials is the development of macular neovascularization (MNV) (inclusive of all types), which was notably higher in all treatment arms compared to sham (GATHER1 (12 months): 9.0% (2 mg) and 9.6% (4 mg) vs. 2.7% (sham); GATHER1 (18 months): 11.9% (2 mg) and 15.7% (4 mg) vs. 2.4-2.7% (sham); GATHER2: 6.7% (2 mg) vs. 4.1% (sham))[9,19,20].

Table 2. Key findings of clinical trials assessing the safety of avacincaptad pegol

Intervention	Subjects	Safety results	Development stage and trial ID
Avacincaptad pegol (0.3, 1 and 2 mg) + ranibizumab (0.5 mg)	subfoveal CNV secondary to AMD	- no dose-limiting toxicity - the majority of reported AEs were linked to the injection procedure	Phase I NC T00709527 [Ref 22]
Avacincaptad pegol (2 mg) + ranibizumab (0.5 mg)	nAMD	- improved visual acuity - TEAEs were related to the injection procedure - one subject experienced retinal detachment and was not linked to the study drug	Phase IIa NC T03362190 [Ref 23, 24]
Avacincaptad pegol (0.3 and 1 mg)	GA	avacincaptad pegol is well tolerated with no associated AEs	Phase I/II NC T00950638 [Ref 25]
Avacincaptad pegol (2 and 4 mg)	GA	- higher incidence of TEAEs in the study groups compared to sham - no serious ocular AEs - (serious) systemic TEAEs were reported - in the updated analysis (after 18 months), one patient of each treatment group experienced a serious AE in the study eye	Phase III NCT 02686658 (GATHER1) [Ref 9, 19]
Avacincaptad pegol (2 mg)	GA	- higher incidence of TEAEs in the study groups compared to sham - serious ocular AEs: choroidal neovascularisation (0.9% vs. 0.5% (sham)) and reduced visual acuity (0.5% of the sham cohort) - (serious) systemic TEAEs were reported	Phase III NCT 04435366 (GATHER2) [Ref 20]

6. Real-world data

The GATHER trials provide no data on patients with pre-existing nAMD undergoing avacincaptad pegol treatment for GA, as this group was excluded from the study design. Retina specialists frequently encounter patients with nAMD who also present with concurrent GA. This condition poses a significant risk of central vision loss or has emerged as the primary factor contributing to the patient's vision loss. Rush et al.

investigated this aspect in a retrospective, case-controlled assessment of pre-existing nAMD patients undergoing avacincaptad pegol treatment for GA. In this real-world study, patients were categorized into two groups: A study group, which included individuals with "stable" or "inactive" nAMD, and a control group, which comprised patients diagnosed with "dry" AMD who had no history of CNV or exudation before beginning avacincaptad pegol treatment for GA. The study and control group patients had a baseline visual acuity of $\geqslant$ 20/200, a total GA lesion area of 1.0 - 17.5 mm^2, and a follow-up period of 12 months after the initiation of avacincaptad pegol. The outcomes of this 12-month study were in favor of the control cohort. The study Group had a greater decrease in visual acuity, a greater increase in GA lesion growth, and a higher incidence of exudation[27] (**Table 3**). Later, the same research group reported real-world outcomes at 12 months in patients who developed MNV while undergoing avacincaptad pegol treatment for GA secondary to AMD. The study consisted of two arms: a study group of subjects who developed MNV and received anti-VEGF therapy during the 12-month period following the initiation of avacincaptad pegol treatment, and a control group of subjects who remained free of complications after starting avacincaptad pegol therapy. The study group had worse clinical outcomes despite undergoing anti-VEGF therapy compared to the control group (**Table 3**)[28]. Both studies highlight the seriousness of MNV in this patient population and provide specialists with crucial information for counseling their patients regarding treatment options for GA secondary to AMD[27,28].

Table 3. Key findings of real-world studies assessing the clinical outcomes of avacincaptad pegol in patients with pre-existing/new-onset nAMD.

Outcomes	Pre-existing nAMD patients undergoing avacincaptad pegol treatment for GA[27]		Patients developing MNV while undergoing avacincaptad pegol treatment for GA secondary to AMD[28]	
	Study group	Control	Study group	control
LogMAR	-0.2	-0.04	-0.22	-0.06
GA lesion growth	1.36	0.52	1.78	0.78
Recurrent exudation*	50.0%	9.4%	-	-

* 50.0% of the study group experienced recurrent exudation vs. 9.4% in the control cohort who experienced CNV development and exudation.

7. Discussion

Since the approval of pegaptanib, the first aptamer drug for the treatment of AMD, in 2004, avacincaptad pegol has distinguished itself as the second aptamer to achieve regulatory approval. This complement inhibitor received FDA approval in 2023 for the treatment of GA secondary to AMD. In 2018, a randomized, double-masked phase IIb trial (NC T03364153) was initiated, with an anticipated enrollment of 120 subjects diagnosed with Stargardt disease type 1 (STGD1)[29]. The primary endpoint of the study is to assess the mean change in the area of the ellipsoid zone defect in patients administered avacincaptad pegol compared to a sham treatment group after 18 months. Given the analogous activation of the complement pathway in both AMD and STGD1, it is plausible to expect a similar outcome regarding the reduction of atrophic growth rate in STGD1 patients.

However, the marketing authorization application submitted to the European Medicines Agency (EMA) was withdrawn in October 2024. The withdrawal was based on findings that, while the treatment successfully slowed the growth of GA lesions, it did not provide a clinically meaningful visual improvement[30]. As a result, avacincaptad pegol is currently approved only in the United States[11].

It seems to be clear that the clinical benefits of avacincaptad pegol remain uncertain based on the current results derived from both the GATHER clinical trials and real-world studies. This uncertainty may arise from various factors, including the measurement methodologies used, the importance of the location of the GA lesion (in addition to its size), and the potential overestimation of the role of the complement

system in disease progression. A *post hoc* analysis of the GATHER trial data suggests that further investigation may significantly enhance our understanding of avacincaptad pegol's efficacy. While avacincaptad pegol appears to exhibit good tolerability, the serious concern regarding MNV conversion in this patient population underscores the necessity for careful monitoring of patients receiving this treatment. However, an in-depth analysis of this tendency may provide a more comprehensive understanding of the interplay between GA treatments, the complement system, and GA progression.

8. Conclusion

GA continues to be the leading cause of irreversible central vision loss, often resulting in legal blindness and significantly impairing quality of life. The identification and management of patients with GA have been challenging due to a lack of effective treatments and insufficient knowledge regarding early diagnosis. Timely intervention is crucial for maximizing the chances of maintaining vision and improving overall quality of life. The C5 complement inhibitor aptamer, avacincaptad pegol, offers hope for those affected by GA. By slowing the progression of GA lesions, this treatment may decrease the risk of severe vision loss over time. However, further investigations are necessary, as the current data remains inconclusive regarding its potential to show a clinically significant visual improvement in visual acuity. Furthermore, the observed increase in the incidence of MNV, along with the associated risks of side effects related to the drug's route of administration, raises critical concerns about the clinical benefits of this treatment.

Looking ahead at the prospects for this second approved aptamer, it is worth recalling the first approved aptamer, pegaptanib. Pegaptanib experienced rapid marginalization following its introduction, primarily due to its inferior efficacy compared to anti-VEGF monoclonal antibodies. It remains premature to ascertain whether avacincaptad pegol will follow a similar trajectory due to the same reason (efficacy) or a different reason (safety).

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