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New horizons in geographic atrophy treatment: enthusiasm and caution surrounding complement inhibitors

Eric Lai,[1] Timothy Lee,[2] Claire Lee,[3] Sidney A Schechet [3]

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[1]Ophthalmology and Visual Science, Yale School of Medicine, New Haven, Connecticut, USA
[2]Ophthalmology, Walter Reed National Military Medical Center, Bethesda, Maryland, USA
[3]Elman Retina Group, Baltimore, Maryland, USA

Correspondence to
Dr Sidney A Schechet; schechets@gmail.com

INTRODUCTION

Current literature estimates that around 196 million people around the world have age-related macular degeneration (AMD), making AMD the leading cause of blindness in adults greater than 50 years of age in developed countries.[1] Geographic atrophy (GA) is characterised by progressive degenerative lesions of the retina in the advanced stages of non-exudative AMD. These atrophic lesions are typically caused by the death of photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris.[2] Although the mechanism is not fully understood, the pathophysiology of GA is well documented to involve the complement system, where overactivation of complement components leads to opsonisation and induction of inflammatory cytokines, resulting in the destruction of the aforementioned structures.[3] One of the hallmark features of exudative AMD is choroidal neovascularisation (CNV), characterised by abnormal growth and leakage of choroidal vasculature breaking through Bruch's membrane, triggered by the activation of vascular endothelial growth factor (VEGF).[4] Multiple therapies are available for exudative AMD, with intravitreal anti-VEGF drugs being the most widely used.[5]

AMD is a complex, multifactorial disease with various environmental and genetic risk factors associated with disease development. Risk factors that predispose patients to GA include age, race, family history and smoking history.[6 7] Once GA begins, the rate of progression and areas to be affected are unpredictable, slow and irreversible. With the progressive spread of these atrophic lesions to involve the fovea, patients will experience irreversible central vision loss.[8] Current literature reports that the median enlargement rate of GA is 2.1 mm^2 per year,[7] while the deterioration of visual acuity in patients with GA due to legal blindness was quantified to a median of 6.2 years.[9]

To monitor the progression of GA, the main imaging modalities include fundus autofluorescence to visualise changes in the RPE, ocular coherence tomography to analyse morphological changes within each layer of the retina and microperimetry to assess macular function.[10] Recent studies show promise in using deep-learning models to predict GA progression; however, more data is necessary prior to clinical implementation.[11]

Historically, there were no treatment options for GA besides conservative measures such as smoking cessation and multivitamins to help reduce the risk of progression.[12] In 2023, two complement-inhibiting agents, pegcetacoplan (Syfovre) and avacincaptad pegol (Izervay), were approved by the Food and Drug Administration (FDA) for use in patients with GA secondary to non-exudative AMD, marking a significant paradigm shift.[13 14] Here, we highlight crucial and controversial findings in respective phase III clinical trials, compare similarities and differences between agents and discuss the potential future implications of these drugs in treating GA.

Complement inhibitors approved for GA treatment

With its approval in early 2023, pegcetacoplan (Syfovre), a C3 and C3b inhibitor, became the first FDA-approved drug for GA treatment. Two phase III trials, OAKS and DERBY, investigated the efficacy of pegcetacoplan on patients with GA through four randomly assigned groups: 15 mg pegcetacoplan injections monthly, pegcetacoplan injections every other month (EOM), sham injections monthly and sham injections EOM.[13]

At 24 months, OAKS found a 22% (–0.90 mm^2) and 18% (–0.74 mm^2) decrease in the growth of GA lesions in those who received pegcetacoplan monthly and EOM, respectively, compared with sham. At 24 months, DERBY showed a 19% (–0.75 mm^2) and 16%

(–0.63 mm^2) decrease in GA lesion growth with monthly and EOM pegcetacoplan injections, respectively, compared with sham. Both studies combined showed a 21% (–0.82 mm^2) and 17% (–0.69 mm^2) decrease in the growth of GA lesions with pegcetacoplan monthly injections and EOM, respectively, versus sham (table 1). The growth difference between monthly versus EOM increases by 1% every 6 months until month 18, past which the growth difference differs by 6% at month 24.

However, both studies failed to show improvement in functional visual outcomes at 24 months, with no significant differences seen in best-corrected visual acuity (BCVA), functional reading independence index scores, mean threshold sensitivity by mesopic microperimetry or the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) distance activity subscale between the pegcetacoplan treatment and sham groups.[13] Regarding safety, for OAKS and DERBY combined, there was a 0.24% rate of intraocular inflammation (IOI), including reports of retinal vasculitis and a 0.03% rate of infectious endophthalmitis, that is, at 24 months. Of note, there was a 1.7% risk of ischaemic optic neuropathy (ION) in the monthly treated group compared with that of 0.2% in the EOM group at 24 months.

Interestingly, at the end of 24 months, new-onset exudative AMD was reported in 11%, 8% and 2% of OAKS patients and 13%, 6% and 4% of DERBY patients receiving pegcetacoplan monthly, EOM and sham, respectively. Despite the first-ever effectiveness of pegcetacoplan in decreasing the rate of GA, the side effect profile with its lack of functional improvements has stirred debates throughout the retina community.

In June 2024, the combined GALE study examining the efficacy of pegcetacoplan over 36 months was presented at the Clinical Trial Summit Meeting.[15] Overall, treatment with pegcetacoplan either monthly or EOM yielded a 25% (–1.49 mm^2) and 20% (–1.21 mm^2) reduction, respectively, compared with the respective projected sham treatment intervals at the end of 36 months. In patients without subfoveal GA involvement, monthly or EOM pegcetacoplan delivered a 42% and 28% reduction, respectively, in the mean growth rate between the 24-month and 36-month periods. For patients with subfoveal GA involvement, treatment with pegcetacoplan monthly or EOM yielded a 31% and 25% reduction, respectively, in the rate of growth of the GA lesion compared with the respective projected sham treatment intervals. In terms of safety through the 36-month mark, there was a total adverse rate of 0.03% for IE and 0.28% for IOI, with no further reports of retinal vasculitis between the 24-month and 36-month marks. Additionally, treatment with pegcetacoplan through the 36-month period showed the development of fewer scotomatous points on microperimetry for monthly (p=0.0156) and EOM (p=0.1233) treatment groups, making Syfovre the first-approved GA therapy to demonstrate visual function benefit at 36 months.

Similarly, avacincaptad pegol (Izervay) is a complement factor C5 inhibitor approved by the FDA in late 2023 for the treatment of GA following its phase III clinical trial, GATHER2.[14] Of note, the scope of the GATHER2 study did not include patients with subfoveal GA in comparison to that of the OAKS and DERBY trials. In GATHER2, patients with GA were randomly assigned to two groups: the monthly avacincaptad pegol 2 mg treatment group or the sham group. At the end of the 12-month study period, the monthly avacincaptad pegol treatment group had a significantly slower GA growth rate, with a mean GA growth rate of 0.336±0.032 mm/year in comparison to that of the sham treatment group, with a growth rate of 0.392±0.033 mm/year. The difference in growth between treatment and sham groups resulted in a difference of 0.056 mm/year or 14%.[14] However, there were no significant differences in BCVA and low-luminance BCVA when comparing avacincaptad pegol and sham groups.

There were no adverse effects of retinal vasculitis, IOI or ION in GATHER2. Interestingly, patients in the avacincaptad pegol treatment group also developed greater rates of macular neovascularisation compared with the sham group, with 15 patients (7%) compared with 9 patients (4%), respectively, and exudative macular neovascularisation occurring in 11 patients (5%) in the treatment group and 7 patients (3%) in the sham group.

In April 2024, the 24-month results for the GATHER 2 trial were announced, revealing that avacincaptad pegol continued to lower the rate of GA lesion growth over 24 months compared with sham.[16] Monthly and EOM dosing demonstrated a 14% and 19% reduction in GA growth at 24 months compared with sham treatments, respectively, doubling the treatment effect over 2 years. Consistent with the 12-month results, there were no cases of retinal vasculitis or ION. However, CNV rates were slightly higher in the monthly group, with reports of 7.4% in 24 months compared with 4% in 12 months, while the CNV rates in the EOM group were stable at around 5% in both 12-month and 24-month data.

DISCUSSION

The FDA approval of both pegcetacoplan and avacincaptad pegol serves as a monumental step in the treatment of GA in advanced AMD. Both agents inhibit the complement pathway involved in AMD, although there are different steps in the pathway. Pegcetacoplan inhibits C3 and C3b, which are complement factors involved earlier in the cascade, compared with avacincaptad pegol, which inhibits the downstream C5 complement factor (figure 1).[13 14]

Fleckenstein *et al* have shown that the rate of progression for GA can range from 0.53 mm^2/year to 2.6 mm^2/year, with a median of 1.78 mm^2/year in linear progression.[17] At their respective endpoints, all studies (OAKS, DERBY, GALE and GATHER2) revealed a significant decrease in GA growth rate in the treatment groups compared with sham groups, demonstrating promising results in delaying GA growth rates.[13 14] However, neither

Table 1 Efficacy endpoints and adverse effect profiles of pegcetacoplan and avacincaptad pegol in various clinical phase III studies

		Pegcetacoplan (Syfovre)				Avacincaptad pegol (Izervay)			
Mechanism of action		C3 and C3b Inhibitor				C5 Inhibitor			
Efficacy endpoints:		OAKS	DERBY	OAKS+DERBY	GALE	GATHER2			
monthsnthly injections	12 months	21%	12%	16%	---	12 months	14%		
(percent decrease in GA lesions)	24 months	22.00%	19.00%	21.00%	---	24 months	14%		
	36 months	---	---	---	25%				
Efficacy endpoints: EOM		OAKS	DERBY	OAKS+DERBY	GALE	GATHER2			
Injection	12 months	16%	11%	14%	---	12 months	---		
(percent decrease in GA lesions)	24 months	18%	16%	17%	---	24 months	19%		
	36 months	---	---	---	20%				
Rate of intraocular	12 months (OAKS+DERBY)			0.22%			0%		
Inflammation (IOI)	24 months (OAKS+DERBY)			0.24%					
	36 months (GALE)			0.28%					
Rate of endophthalmitis	12 months (OAKS+DERBY)			0.05%			0%		
	24 months (OAKS+DERBY)			0.03%					
	36 months (GALE)			0.03%					
New onset exudative AMD			MONTHLY	EOM	SHAM		MONTHLY	EOM	SHAM
	OAKS (24 months)		11%	8%	2%	12 months	4%	5%	3%
	DERBY (24 months)		13%	6%	4%	24 months	7%	5%	---
	OAKS+DERBY (24 months)		12%	7%	3%				
	GALE (36 months)		20%	9%	7%				

AMD, age-related macular degeneration; EOM, every other month; GA, geographic atrophy.

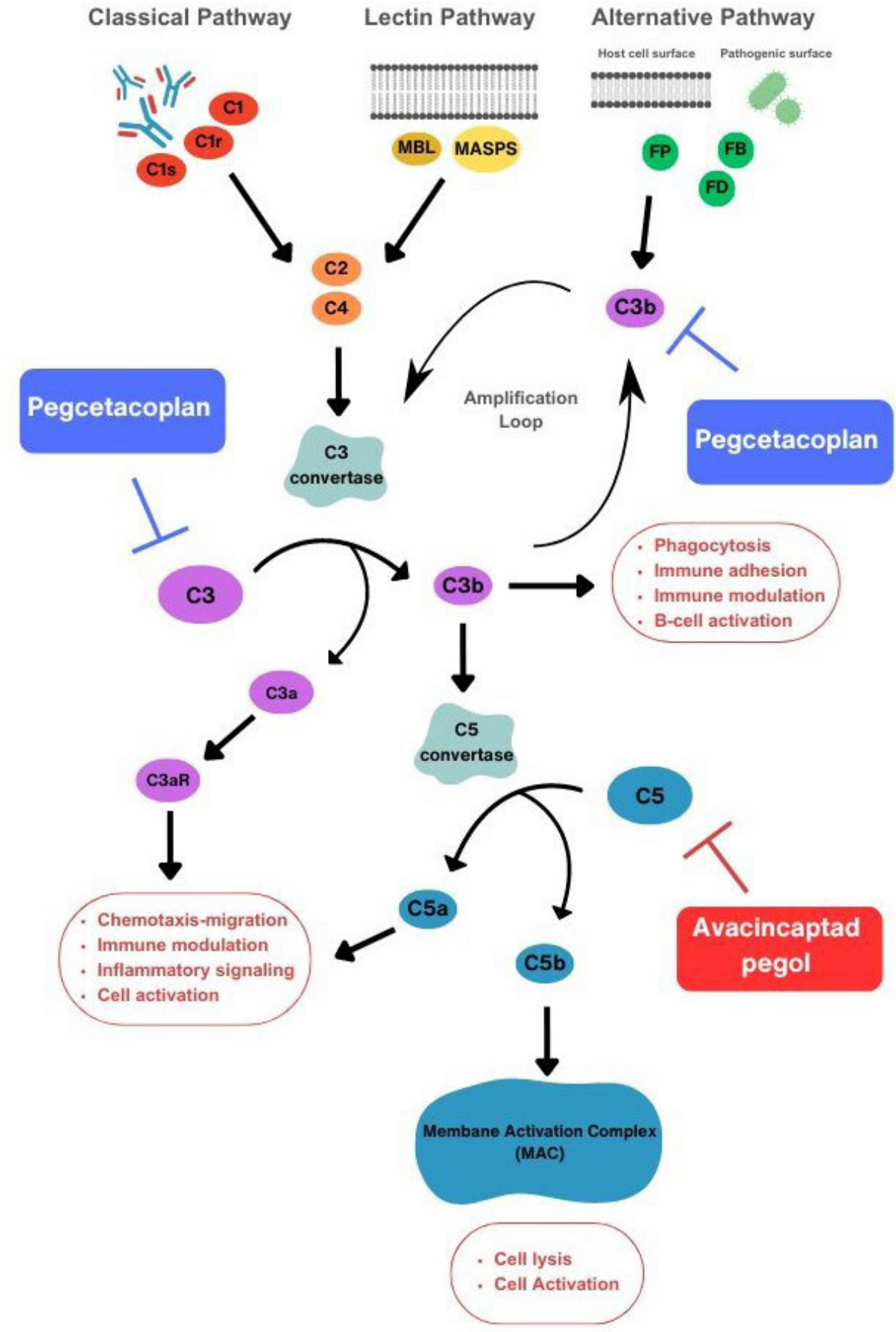

Figure 1 Pegcetacoplan and avacincaptad pegol mechanisms of action in complement cascade inhibition.

agent demonstrated an overall significant improvement in functional outcomes in either treatment group at the end of their respective primary endpoints. The only significant improvement in visual function was the development of fewer scotomatous points from monthly pegcetacoplan use in the 36-month GALE extension trial.[15] Due to the overall lack of functional benefits, some retina specialists question whether the benefits of treatment with these novel agents outweigh the risks of potential complications and the significant burdens that may arise with receiving regularly scheduled intravitreal injections.[18 19] Furthermore, a recent meta-analysis by Lin *et al* questions the role of the complement cascade in the pathogenesis of GA.[20] Regardless, the aforementioned studies have demonstrated the role of complement inhibitors in reducing the rate of GA. Further long-term data regarding the impact of these novel agents on patients' visual function and other metrics would be necessary to see if there is an actual benefit to quality of life.[21]

A large concern in all studies is the finding of new-onset exudative AMD or CNV conversion observed in both agents.[13 14] Although the association between complement inhibition and CNV development remains unclear, perhaps patients with pre-existing subclinical CNV are potentially unmasked in those receiving complement inhibitor agents. Another theory is that given VEGF's role in CNV development, perhaps treatment of eyes with GA may result in surviving cells continuously producing VEGF, leading to a higher risk of CNV development.[22]

Additionally, retinal vasculitis has been reported in association with pegcetacoplan since its launch. On 15 July 2023, the American Society of Retina Specialists Research and Safety in Therapeutics committee issued an update on adverse events of IOI and retinal vasculitis following pegcetacoplan injection. Witkin *et al* confirmed 14 eyes of 13 patients diagnosed with retinal vasculitis resulting in vision loss after receiving the first pegcetacoplan injection, including two eyes requiring enucleation.[23] The aetiology of retinal vasculitis after pegcetacoplan injection remains unknown. As a result, an additional extension of the phase III trial, GALE, was initiated as an extension of prior studies to continue monitoring and reporting of adverse effects. These findings highlight that in patients receiving complement inhibitor treatment, particularly for treatment-naive eyes, close monitoring is required for the potential development of CNV and other adverse effects.[23] At this time, no postapproval real-world data have been published on these adverse events as well as reports of vasculitis as a result of avacincaptad pegol administration.

Another key point in the discussion is that currently, there are no standardised guidelines for the diagnosis and treatment of GA among eyecare providers. Since extrafoveal GA lesions can progress more rapidly than foveal lesions, early identification and intervention in the GA disease course are critical. While the OAKS and DERBY studies included eyes with foveal-involving GA, the GATHER2 study with avacincaptad pegol did not include patients with foveal involvement, potentially reflective of GA in earlier presentations or newly diagnosed patients. GA size, stage and location are important when considering treatment options,[24] with pegcetacoplan having evidence of delaying GA growth in patients with subfoveal and extrafoveal lesions, while avacincaptad pegol may be more suitable for patients with non-foveal lesions based on current data. Avacincaptad pegol currently appears to have a more favourable safety profile compared with pegcetacoplan, pending real-world data since launch. Additionally, there are currently no standardised prognostic comparative imaging modalities to follow the therapeutic responses in a clinical setting. While GA can be confirmed with imaging, it is difficult to track progression in the clinic and demonstrate to patients these agents' efficacy and clinical course with and without treatment.

In the retinal community, complement inhibitor agents represent a promising frontier in treating GA; however, there remains scepticism and concern about these drugs' overall effectiveness and risks.[25] The decision to offer these agents involves a nuanced risk-benefit assessment. While the long-term safety profile of these agents is still being evaluated, raising uncertainties about their overall tolerability and durability of treatment effects, our current approach is to not offer these agents to patients with significant comorbidities or high risk of wet AMD conversion, including those with wet AMD in the fellow eye, fibrovascular pigment epithelial detachment and a history of active smoking, retinal vasculitis or ION. Additionally, the financial burden associated with novel therapies can be considerable, adding another layer of consideration. Conversely, the potential benefits of complement inhibitors include their ability to slow or halt the progression of GA, thereby preserving vision and improving quality of life for affected individuals.

Ultimately, the decision whether to offer complement inhibitors calls for an individualised approach to each patient. Our approach is to educate and inform patients about this new treatment option, with in-depth discussions on its potential efficacy and adverse effects, followed by shared decision-making with patients if they'd like to pursue this option. Until further data establishes their efficacy and safety conclusively, clinicians may opt for established treatments or supportive care measures. This approach ensures that patient care remains balanced and informed, prioritising both safety and the potential for meaningful therapeutic outcomes.

CONCLUSION

Pegcetacoplan (Syfovre) and avacincaptad pegol (Izervay) are the first and only FDA-approved intravitreal therapies for the treatment of AMD-associated GA, with both agents demonstrating promise in decreasing the growth rate of GA lesions. The current utilisation of either agent in clinical practice is limited by the lack of significant improvement in visual functional outcomes and association with treatment-adverse events, including

the development of CNV, ischaemic optic neuropathy and intraocular inflammation. The development of these agents has inspired new hope for both clinicians and patients alike for battling against the previously untreatable GA disease. While the retinal community continues to debate the feasibility and treatment algorithms with these novel agents, further studies are necessary to closely monitor the long-term efficacy and safety profile of these agents, as well as advance the field with newer generation complement inhibitors to offer a wider selection of therapeutic options in treating GA.

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ORCID iD

Sidney A Schechet http://orcid.org/0000-0001-8996-3855

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