Complement inhibitors in AMD: a Cochrane systematic review and meta-analysis

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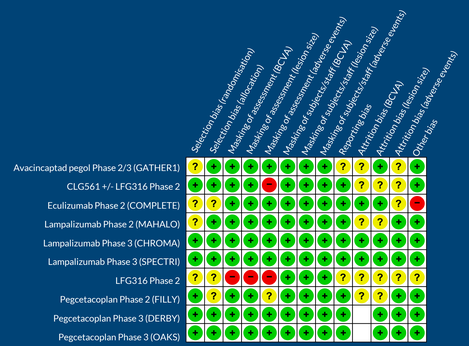
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Introduction

- Age-related macular degeneration (AMD) is a leading cause of blindness globally, and the complement system has been implicated in its pathogenesis.
- Neovascular AMD (nAMD) and geographic atrophy (GA) are advanced subtypes.
- Until recently, there were no AMD treatments that target underlying degeneration.
- Strategies to suppress retinal inflammation include blocking complement activation (C3 or C5) or supplementing endogenous regulatory activity.
- **The aim of this review was to assess the effects and safety of complement inhibitors in the prevention/treatment of advanced AMD.**

Methods

- We searched multiple databases until 29 June 2022, and contacted companies for unpublished data.
- We included RCTs with parallel groups, comparator arms, and follow-up duration of 12 weeks or more.
- Two authors independently assessed search results and graded the risk of bias & evidence certainty for each study, with arbitration by a third author.
- We evaluated various outcome measures including changes in best-corrected and low luminance visual acuity (BCVA; LLVA), GA lesion size progression, development of nAMD or endophthalmitis, and change in quality of life (QoL) **at one year**.



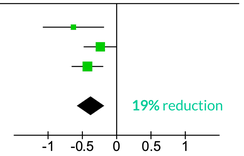
The overall risk of bias was low.

C3 and C5 inhibitors have shown **anatomical, but not functional, benefits** in treating geographic atrophy

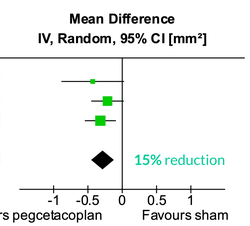
Cochrane

Pegcetacoplan meaningfully reduces GA lesion size growth at 1 year (high certainty ⊕⊕⊕⊕)

Study or Subgroup	Pegcetacoplan 4-weekly Mean [mm²]	SD [mm²]	Total	Sham 4-weekly Mean [mm²]	SD [mm²]	Total	Mean Difference IV, Random, 95% CI [mm²]
Pegcetacoplan Phase 2 (FILLY)	1.49	1.47	84	2.12	1.44	80	-0.63 [-1.08 , -0.18]
Pegcetacoplan Phase 3 (DERBY)	1.73	1.12	201	1.968	1.33	194	-0.24 [-0.48 , 0.01]
Pegcetacoplan Phase 3 (OAKS)	1.546	1.19	202	1.972	1.18	206	-0.43 [-0.66 , -0.20]
Total (95% CI)			**487**			**480**	**-0.38 [-0.57 , -0.19]**

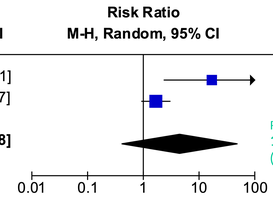


Study or Subgroup	Pegcetacoplan 8-weekly Mean [mm²]	SD [mm²]	Total	Sham 8-weekly Mean [mm²]	SD [mm²]	Total	Mean Difference IV, Random, 95% CI [mm²]
Pegcetacoplan Phase 2 (FILLY)	1.69	1.48	78	2.12	1.44	80	-0.43 [-0.89 , 0.03]
Pegcetacoplan Phase 3 (DERBY)	1.753	1.05	200	1.968	1.33	194	-0.22 [-0.45 , 0.02]
Pegcetacoplan Phase 3 (OAKS)	1.653	1.15	205	1.972	1.18	206	-0.32 [-0.55 , -0.09]
Total (95% CI)			**483**			**480**	**-0.29 [-0.44 , -0.13]**

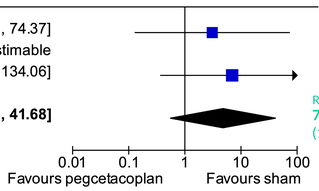


Pegcetacoplan ***may*** meaningfully increase the risk of nAMD at 1 year (low certainty ⊕⊕◯◯)

Study or Subgroup	Pegcetacoplan 4-weekly Events	Total	Sham 4-weekly Events	Total	Risk Ratio M-H, Random, 95% CI
Pegcetacoplan Phase 2 (FILLY)	18	86	1	81	16.95 [2.32 , 124.11]
Pegcetacoplan Phase 3 (DERBY & OAKS)	27	419	16	417	1.68 [0.92 , 3.07]
Total (95% CI)		**505**		**498**	**4.47 [0.41 , 48.98]**
Total events:	45		17		



Study or Subgroup	Pegcetacoplan 8-weekly Events	Total	Sham 8-weekly Events	Total	Risk Ratio M-H, Random, 95% CI
Pegcetacoplan Phase 2 (FILLY)	1	79	0	81	3.08 [0.13 , 74.37]
Pegcetacoplan Phase 3 (DERBY)	0	208	0	206	Not estimable
Pegcetacoplan Phase 3 (OAKS)	3	212	0	211	6.97 [0.36 , 134.06]
Total (95% CI)		**499**		**498**	**4.77 [0.55 , 41.68]**
Total events:	4		0		



Results

- We screened 2521 records, including 10 studies (4,052 participants w/ GA)
- All 10 included studies evaluated C3, C5, or FD inhibition vs sham/placebo
- All agents except one (Eculizumab) were intravitreally administered
- **Lampalizumab** (FD inhibitor) had no meaningful effect on BCVA, GA lesion size progression, LLVA, or QoL. It may have increased risk of nAMD (19 per 1000), and probably increased risk of endophthalmitis (3 or 4 per 1000)
- **Pegcetacoplan** (C3 inhibitor) improved GA lesion size growth, but probably had no meaningful benefit on BCVA or LLVA. It may have also increased the risk of nAMD, and probably increased the risk of endophthalmitis (6 or 8 per 1000).
  Functional data from Phase 3 studies were unavailable at time of analysis.
- **Avacincaptad pegol** (C5 inhibitor) probably reduced GA lesion growth, but probably had no meaningful effect on BCVA or LLVA. It may have increased the risk of nAMD (RR 3.13, 95% CI 0.93 to 10.55). There were no reports of endophthalmitis.
  GATHER2 (Phase 3) study data were unavailable at time of analysis.
- **Eculizumab** (C5 inhibitor), **LFG316** (C5 inhibitor), and **CLG561** (properdin inhibitor) had no anatomical or functional benefits.

Discussion

- Despite confirmation of the negative findings of intravitreal lampalizumab across all endpoints, local complement inhibition with intravitreal pegcetacoplan meaningfully reduces GA lesion growth relative to sham at one year.
- Inhibition of complement C5 with intravitreal avacincaptad pegol is also an emerging therapy with probable benefits on anatomical endpoints in extrafoveal/juxtafoveal GA.
- There is currently no evidence that complement inhibition with any agent improves functional endpoints in advanced AMD; further results from Phase 3 studies of pegcetacoplan and avacincaptad pegol are eagerly awaited.
- Progression to MNV or exudative AMD is a possible emergent adverse event of complement inhibition, requiring careful consideration in patients.
- Intravitreal administration of complement inhibitors is probably associated with a small risk of endophthalmitis, which may be higher than other intravitreal therapies.

Conclusions

- Many therapeutic strategies are being investigated for the treatment of GA, but not many have progressed to Phase 3.
- The leading drug candidates (pegcetacoplan and avacincaptad pegol) have demonstrated anatomical but not visual benefit.
- The optimal dosing regimens, treatment duration, and cost-effectiveness of such therapies are yet to be established.
- One approach may not fit all patients.

Reference

- Tzoumas et al., Complement inhibitors for age-related macular degeneration, Cochrane Database Syst Rev, 2023 (In Press)

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NT and **GR**, no disclosures; **MW**, ad hoc speaker for AbbVie, Novartis and Bayer, education grant from Bayer; **DHS**, Alcon (C, F), Bayer (F), Boehringer Ingelheim (F), BVI Medical (C), DORC (C, F), Gyroscope Therapeutics (C), Roche (C).

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