Complement Targeted Therapies in AMD

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1.0 – Introduction

Age-related macular degeneration (AMD) is a progressive retinal disease and a leading cause of central vision loss in older adults. With global cases expected to rise to 288 million by 2040, effective treatment is a growing public health need[1].

AMD affects the macula, damaging photoreceptors and the retinal pigment epithelium (RPE) - impairing reading, facial recognition, and overall independence.

Early AMD is marked by drusen accumulation and RPE changes; late AMD includes:
- Dry AMD (geographic atrophy) – slow degeneration of RPE
- Wet AMD (choroidal neovascularisation) – rapid vision loss due to VEGF-driven vessel growth

Approved treatments (Pegcetacoplan & Avacincaptad Pegol) inhibit C3 and C5 to slow progression[2].

Complement dysregulation and genetic susceptibility are central to AMD pathogenesis and therapeutic development.

1.1 – AMD Pathogenesis

Risk factors include:
- Age (strongest)
- Genetics
- Smoking
- Oxidative stress

Bruch's membrane (BrM) thickens with age, impeding nutrient exchange and enabling drusen formation.

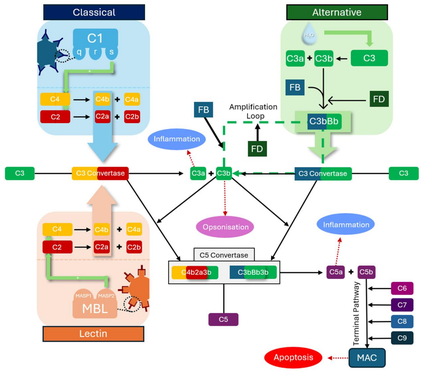


Figure 1 *– Diagram of the complement system and the pathways involved.*

MBL *= Mannose Binding Lectin,* ***MASP1*** *= Mannose-Associated Serine Protease 1,* ***MASP2*** *= Mannose-Associated Serine Protease 2,* ***FD*** *= Factor D,* ***FB*** *= Factor B,* ***MAC*** *= Membrane Attack Complex*

1.2 – The Complement System in AMD

The complement cascade defends against pathogens but in AMD, dysregulation (especially of the alternative pathway) leads to chronic inflammation and cell death.

Three pathways converge at C3 convertase, leading to C5 cleavage and membrane attack complex (MAC) formation (see **Figure 1**).

Protective regulators like Factor H and CD59 normally suppress overactivation:

- CD59: blocks MAC formation; under clinical investigation as therapy.
- Factor H: inhibits C3b amplification; its dysfunction promotes disease.

1.3 – Genetics & AMD

Genetic mutations affect complement regulation:
- CFH Y402H: reduces Factor H binding → uncontrolled complement activation
- HTRA1/ARMS2: promotes BrM breakdown and RPE inflammation
- Non-coding SNPs increase FHR protein levels, reducing C3b turnover → complement activation

Gene therapy is being explored to:
- Supplement missing/defective regulators
- Silence harmful gene variants via RNA interference (RNAi)
- Cemdisiran targets C5
- ARO-C3 targets C3[3].

Aims

This systematic review aims to identify current complement-targeted therapies for dry AMD and evaluate their clinical efficacy.

Objectives
- Outline the role of the complement cascade and genetics in AMD pathogenesis
- Review existing complement-targeted therapies for dry AMD
- Identify the most effective points of intervention within the cascade
- Highlight knowledge gaps and suggest directions for future research

2.0 – Methods

Databases Searched:
- PubMed – search terms: AMD AND Complement AND Therapy
- ClinicalTrials.gov – Condition: Age-related macular degeneration, Intervention: Complement

Selection Process:
Duplicate results were removed, and remaining studies underwent manual screening for relevance.

Inclusion Criteria:
- ✓ English language
- ✓ Free full-text access
- ✓ Human studies reporting therapeutic interventions

Exclusion Criteria:
- ✗ Animal studies
- ✗ Non-interventional studies
- ✗ Irrelevant focus to complement-based therapies

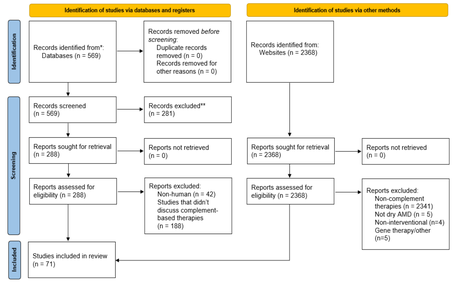


Figure 2 – PRISMA diagram outlining the steps taken to obtain studies for this systematic review.

3.0 - Results

A total of 569 studies were initially identified from PubMed, narrowed to 58 after screening for relevance and eligibility (see **Figure 2**). From ClinicalTrials.gov, 2368 trials were found; filtering for complement-based interventions in dry AMD yielded 13 relevant trials. Altogether, 71 studies were included in this review.

3.1 - C3 Targeted Therapies

- **Pegcetacoplan** (APL-2) was the most studied C3 inhibitor (used in 5 trials).
  - FILLY: 20–29% reduction in GA growth; however, increased risk of wet AMD[4].
  - OAKS & DERBY: Phase 3 trials showed efficacy, leading to FDA approval[5].
  - GALE: Ongoing long-term study.
- NGM621 (CATALINA trial): Well-tolerated but did not meet efficacy endpoints[6].
- AL-78898A (POT-4): Trial terminated; no results available.
- AMY-101: Early trials suggest potential, with ongoing studies.

3.2 – C5 Targeted Therapies

- **Avacincaptad Pegol**:
  - GATHER1 & GATHER2: ~17–28% reduction in GA growth; FDA approved[7].
  - Mild procedural side effects; increased wet AMD risk noted.
- LFG316: Safe but ineffective in reducing GA progression[8].
- Eculizumab: No significant benefit in AMD despite success in other diseases[9].

3.3 – Other Complement Targeted Therapies

- Lampalizumab (anti-CFD):
  - Early trials showed promise, but all phase 3 studies failed to meet endpoints[10].
- Danicoptan (oral CFD inhibitor): Ongoing; results expected 2025.
- CLG561 (properdin inhibitor): Safe but no efficacy in combination or monotherapy.
- GEM103 (recombinant Factor H): Safe, but no added benefit in phase 2; trial terminated.
- IONIS-FB-LRx (CFB antisense): Phase 2 trial ongoing (GOLDEN study).
- ANX007 (C1q inhibitor, classical pathway): Phase 2 ARCHER trial did not meet endpoints[11].

4.0 - Discussion

Promise of Complement-Based Therapies...
- Targeting the complement cascade, especially C3 and C5, shows strong potential in slowing GA in AMD.
- FDA approval of Pegcetacoplan and Avacincaptad pegol reflects this progress.
- Despite mixed trial outcomes, each contributes to refining therapeutic strategies and understanding disease mechanisms.

Need for Broader Targeting Strategies...
- Most trials tested single-target agents; however, combination approaches may better address AMD's complexity.
- The Alcon trial combining C5 and properdin inhibition highlights potential for multi-target therapy, despite unmet endpoints.

Drug Delivery and Patient Preferences...
- Intravitreal injections remain the main delivery route. While effective, they are invasive and may affect long-term adherence.
- Exploring alternative or patient-tailored delivery methods could improve outcomes and engagement.

Long-Term Efficacy & Personalisation...
- Sustained treatment appears necessary for continued benefit.
- Genetic differences may influence drug response, supporting the case for personalised therapies.
- Trials like those evaluating GEM103 and AMY-101 underline the importance of both genotype considerations and representative patient cohorts.

Strengths in Current Research...
- Complement inhibition reduces inflammation and MAC formation, directly addressing AMD pathology.
- Growing trial success supports continued investment and innovation in this area.

Limitations and Challenges...
- No current therapy reverses GA, and some fail to prevent conversion to neovascular AMD.
- Trial diversity and sample sizes vary greatly, limiting how representative these results are of the wider population.
- Additionally, endpoints focused on GA growth may not fully reflect functional vision improvement.

Barriers to Implementation...
- Regular injections, cost, geographic access, and patient comorbidities may hinder uptake, especially in older populations.
- These logistical issues, along with lengthy trial durations, need to be addressed to enhance real-world applicability.

Considerations for Future Research...
- Combination therapies (complement inhibitors/other therapies/lifestyle changes).
- Broader trial demographics and earlier intervention.
- Tailored treatments based on genetic and phenotypic profiling.
- Outcomes that align more closely with quality of life and visual function.

5.0 – Conclusion

Complement-based therapies represent a promising advancement in the treatment of dry AMD. Clinical trials consistently show reduced GA lesion growth, reinforcing the role of complement inhibition in slowing disease progression.
The FDA approval of Pegcetacoplan and Avacincaptad pegol marks a significant milestone. However, long-term safety, efficacy, and accessibility must continue to be evaluated.

Future research should focus on:
- Personalised therapies based on genetic profiles
- Combination treatments targeting multiple disease pathways
- Alternative delivery methods to enhance adherence and accessibility

Addressing the multifactorial nature of AMD including genetic, environmental, and anatomical factors will be essential to developing effective, patient-centred therapies.

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