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INNOVATIVE THERAPEUTIC STRATEGIES IN AGE-RELATED MACULAR DEGENERATION: CURRENT AND FUTURE PERSPECTIVES

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ABSTRACT

Age-related macular degeneration (AMD) is a leading cause of irreversible central vision loss in older adults and an increasing public health challenge. Its pathogenesis involves oxidative stress, chronic inflammation, complement dysregulation, retinal pigment epithelium dysfunction, and pathological angiogenesis. This narrative review summarizes current and emerging therapeutic strategies for AMD, focusing on innovative technologies, durable drug-delivery systems, precision medicine, and artificial intelligence (AI). A literature search was conducted using PubMed, Cochrane Library, Google Scholar, and selected clinical guidelines. Randomized clinical trials, phase 1–3 studies, review articles, translational research, and current recommendations published mainly between 2018 and 2026 were included. Anti-VEGF therapy remains the standard treatment for neovascular AMD, while faricimab enables extended dosing through dual VEGF-A and angiopoietin-2 inhibition. In geographic atrophy, pegcetacoplan and avacincaptad pegol represent the first disease-modifying therapies by slowing lesion progression. Gene therapy, cell-based approaches, the Port Delivery System, nanotechnology, biomarkers, and AI-assisted imaging may further reduce treatment burden and support personalized retinal care. Current AMD management is shifting toward longer-acting, mechanism-based, and technology-supported strategies, although further studies are required to confirm their long-term safety, accessibility, cost-effectiveness, and real-world clinical value.

KEYWORDS

Age-Related Macular Degeneration, AMD, Anti-VEGF, Gene Therapy, Drug Delivery, Artificial Intelligence

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1. Introduction

Age-related macular degeneration (AMD) is a chronic progressive retinal disease and one of the leading causes of irreversible visual impairment in older adults worldwide (Fleckenstein et al., 2024; Guymer & Wu, 2023). It primarily affects the macula, resulting in progressive loss of central vision that compromises reading, driving, facial recognition, and other daily activities, thereby reducing independence and quality of life.

Beyond its clinical importance, AMD represents a growing public health challenge. The disease predominantly affects older adults, who frequently present with multimorbidity, frailty, and reduced mobility, making long-term ophthalmic care more demanding. Global estimates indicate that approximately 196 million individuals were affected in 2020, with prevalence projected to reach nearly 288 million by 2040 (Wong et al., 2014). Consequently, AMD contributes substantially to healthcare utilization, disability, caregiver burden, and reduced social participation.

Clinically, AMD progresses from early and intermediate stages, characterized by drusen and pigmentary abnormalities, to advanced disease. Advanced AMD is classified as non-neovascular (dry) or neovascular (wet) AMD (Fleckenstein et al., 2024; Guymer & Wu, 2023). Dry AMD may progress to geographic atrophy with degeneration of the retinal pigment epithelium (RPE), photoreceptors, and choriocapillaris, whereas neovascular AMD is characterized by abnormal retinal neovascularization, exudation, hemorrhage, fibrosis, and rapid visual deterioration.

AMD pathogenesis is multifactorial, involving aging, oxidative stress, mitochondrial dysfunction, lipid accumulation, complement activation, chronic inflammation, genetic susceptibility, smoking, diet, and cardiovascular risk factors (Fleckenstein et al., 2024; Guymer & Wu, 2023). Advances in understanding these mechanisms have transformed treatment strategies. Anti-VEGF therapy has markedly improved outcomes in neovascular AMD, although frequent intravitreal injections, incomplete response, and undertreatment remain important challenges (Fleckenstein et al., 2024; Vemulakonda et al., 2025). More recently, complement inhibitors have become the first disease-modifying therapies for geographic atrophy, while gene therapy, regenerative medicine, advanced drug-delivery systems, biomarkers, and artificial intelligence (AI) have

emerged as promising future directions (Campochiaro et al., 2024; Crincoli et al., 2024; Heier et al., 2023; Khanani et al., 2023; Rodriguez-Cruz et al., 2025; Sakai et al., 2025).

This review summarizes current therapeutic strategies and emerging technologies in AMD, evaluates their clinical potential and limitations, and discusses future directions in precision retinal medicine. Particular emphasis is placed on technological innovations that may improve treatment durability, reduce patient burden, and support more personalized and sustainable ophthalmic care.

2. Methodology

This narrative review synthesizes current evidence on therapeutic strategies for AMD by integrating data from randomized clinical trials, phase 1–3 studies, translational research, clinical guidelines, and high-quality review articles. A narrative approach was selected because it enables comprehensive evaluation of established therapies alongside emerging technologies at different stages of clinical development.

A structured literature search was performed using PubMed, Cochrane Library, Google Scholar, and selected professional guideline resources. Publications from 2018–2026 were prioritized to capture recent advances, while landmark earlier studies were included to provide epidemiological and conceptual background. Search terms included *age-related macular degeneration*, *AMD*, *neovascular AMD*, *geographic atrophy*, *anti-VEGF*, *faricimab*, *pegcetacoplan*, *avacincaptad pegol*, *RGX-314*, *ixoberogene soroparvovec*, *gene therapy*, *retinal pigment epithelium transplantation*, *Port Delivery System*, *drug delivery*, *nanotechnology*, and *artificial intelligence*. Boolean operators were used to optimize search specificity and sensitivity.

Eligible publications included randomized clinical trials, major phase 1–3 studies, systematic and narrative reviews, professional guidelines, expert recommendations, and translational studies directly relevant to AMD therapy. Non-peer-reviewed publications, conference abstracts without sufficient methodological detail, isolated case reports, and studies with limited methodological quality were excluded.

The selected literature underwent qualitative thematic synthesis organized into the following areas: AMD pathophysiology, current anti-VEGF therapy, limitations of existing treatment, complement inhibition, gene therapy, cell-based therapy, drug-delivery innovations, precision medicine, biomarkers, and AI. Particular attention was given to mechanisms of action, clinical efficacy, safety, treatment durability, and the potential impact of emerging technologies on routine ophthalmic practice and healthcare delivery. The review was conducted in accordance with current recommendations for narrative reviews.

3. Results

3.1. Pathophysiology of AMD

Age-related macular degeneration (AMD) results from progressive dysfunction of interconnected homeostatic mechanisms within the outer retina. Retinal pigment epithelium (RPE) impairment is an early event that disrupts photoreceptor maintenance, nutrient transport, immune regulation, and the outer blood-retinal barrier, leading to accumulation of metabolic debris beneath the RPE (Fleckenstein et al., 2024; Guymer & Wu, 2023).

Drusen, the hallmark of early and intermediate AMD, contain complement proteins, lipids, inflammatory mediators, and cellular waste, reflecting active disease processes rather than passive deposits. Their accumulation impairs Bruch's membrane permeability and promotes chronic inflammation (Guymer & Wu, 2023).

Oxidative stress further accelerates retinal degeneration because the retina is highly susceptible to reactive oxygen species. Mitochondrial damage, impaired autophagy, and apoptosis of RPE cells and photoreceptors contribute to disease progression (Fleckenstein et al., 2024; Guymer & Wu, 2023).

Complement dysregulation plays a central role in dry AMD and geographic atrophy. Variants in complement-related genes, including *CFH* and *C3*, support complement inhibition as a therapeutic target (Fleckenstein et al., 2024; Guymer & Wu, 2023). Progressive degeneration of the RPE, photoreceptors, and choriocapillaris ultimately results in irreversible vision loss.

In neovascular AMD, increased VEGF expression induced by hypoxia, oxidative stress, and inflammation promotes abnormal vessel formation, vascular leakage, hemorrhage, fibrosis, and rapid visual deterioration (Fleckenstein et al., 2024). These mechanisms explain the development of multiple therapeutic strategies, including anti-VEGF agents, complement inhibitors, regenerative therapies, and AI-supported technologies for earlier diagnosis and personalized management.

3.2. Current Standards of Treatment: Anti-VEGF Therapy

Intravitreal anti-VEGF therapy remains the standard treatment for neovascular AMD and has transformed its prognosis from progressive visual loss to long-term stabilization or improvement (Fleckenstein et al., 2024; Vemulakonda et al., 2025).

Currently available agents include ranibizumab, aflibercept, brolucizumab, and faricimab (Fleckenstein et al., 2024; Heier et al., 2022; Khanani, Kotecha, et al., 2024). Although they differ in molecular characteristics and durability, all suppress VEGF-mediated neovascularization. Treatment monitoring relies on best-corrected visual acuity and optical coherence tomography (OCT), which guides detection of disease activity and adjustment of injection intervals.

Ranibizumab established the clinical efficacy of anti-VEGF therapy, whereas aflibercept broadened VEGF inhibition by targeting VEGF-A, VEGF-B, and placental growth factor. Brolucizumab offers prolonged anatomical control but is limited by concerns regarding intraocular inflammation and retinal vasculitis.

Faricimab represents a significant advance by simultaneously inhibiting VEGF-A and angiopoietin-2. In the TENAYA and LUCERNE phase 3 trials, it achieved visual outcomes comparable to aflibercept while extending treatment intervals to as long as 16 weeks in many patients. Two-year follow-up confirmed sustained efficacy using a treat-and-extend regimen (Heier et al., 2022; Khanani, Kotecha, et al., 2024).

Current treatment strategies include fixed dosing, pro re nata, and treat-and-extend protocols, with the latter providing the best balance between efficacy and treatment burden (Vemulakonda et al., 2025). Despite excellent outcomes, anti-VEGF therapy remains suppressive rather than curative, requiring long-term injections. Therefore, therapies that safely extend dosing intervals may improve adherence, reduce healthcare utilization, and decrease patient and caregiver burden.

3.3. Limitations of Current Therapies

Despite their effectiveness, anti-VEGF therapies have important limitations. The need for repeated intravitreal injections places a considerable burden on patients, caregivers, and healthcare systems. Transportation difficulties, reduced mobility, comorbidities, and anxiety may compromise long-term adherence and visual outcomes (Fleckenstein et al., 2024; Vemulakonda et al., 2025).

Clinical outcomes achieved in routine practice are often inferior to those reported in randomized trials because treatment schedules are less consistent and follow-up is frequently delayed. Furthermore, some patients demonstrate persistent or recurrent retinal fluid despite regular therapy, indicating that mechanisms beyond VEGF, including inflammation, fibrosis, and vascular instability, contribute to disease progression (Fleckenstein et al., 2024; Guymer & Wu, 2023; Heier et al., 2022).

Although intravitreal injections are generally safe, they carry risks of endophthalmitis, retinal detachment, intraocular inflammation, and increased intraocular pressure. Importantly, anti-VEGF therapy controls neovascularization but does not prevent the underlying retinal degeneration, allowing macular atrophy or fibrosis to develop over time.

Until recently, no disease-modifying therapy was available for geographic atrophy, which stimulated development of complement inhibitors, regenerative medicine, and sustained drug-delivery systems (Heier et al., 2023; Khanani et al., 2023; Rodriguez-Cruz et al., 2025; Sakai et al., 2025). Future treatment should therefore prioritize not only efficacy but also durability, preservation of retinal structure, improved adherence, and reduced treatment burden.

3.4. Emerging Pharmacological Therapies: Complement Inhibitors

Complement inhibition represents the first disease-modifying pharmacological approach for geographic atrophy (GA) secondary to dry AMD. This strategy is based on genetic and experimental evidence linking complement dysregulation with AMD pathogenesis (Fleckenstein et al., 2024; Guymer & Wu, 2023).

Pegcetacoplan, a C3 inhibitor, significantly slowed GA lesion enlargement in the OAKS and DERBY phase 3 trials, while avacincaptad pegol, a C5 inhibitor, demonstrated similar efficacy in the GATHER2 study (Heier et al., 2023; Khanani et al., 2023). These findings establish complement activation as a clinically relevant therapeutic target and emphasize structural preservation rather than short-term visual acuity improvement.

Although these agents do not restore lost RPE or photoreceptors, they delay disease progression and prolong preservation of functional retinal tissue. Treatment therefore aims to slow atrophy rather than improve vision, making appropriate patient counseling and careful monitoring essential, particularly because of the increased risk of conversion to neovascular AMD in some patients (Heier et al., 2023; Khanani et al., 2023).

Treatment decisions should consider lesion location, progression rate, foveal involvement, and functional status. Despite these limitations, complement inhibitors represent a major advance in the management of dry AMD and have shifted clinical practice from observation toward active intervention.

3.5. Gene Therapy

Gene therapy aims to provide sustained intraocular production of anti-VEGF proteins after a single administration, thereby reducing the need for repeated intravitreal injections (Campochiaro et al., 2024; Khanani, Boyer, et al., 2024). Most current approaches use adeno-associated viral (AAV) vectors because of their favorable safety profile and long-term transgene expression.

Among the leading candidates, RGX-314 delivers an anti-VEGF antibody fragment through subretinal administration. Phase 1/2a studies demonstrated good safety, maintained anatomical and functional outcomes, and reduced requirements for additional anti-VEGF therapy (Campochiaro et al., 2024). Ixoberogene soroparvovec, administered intravitreally, also showed sustained disease control with fewer supplemental injections in the OPTIC study (Khanani, Boyer, et al., 2024).

The principal advantage of gene therapy is long-term biological activity after a single procedure, potentially reducing treatment burden and healthcare utilization. However, important challenges remain, including immune responses, variable transgene expression, procedural risks, long-term safety, and patient selection. Further clinical studies are needed before gene therapy can become part of routine AMD management.

3.6. Cell-Based Therapies

Cell-based therapies are being investigated as regenerative treatments for advanced dry AMD by replacing damaged retinal pigment epithelium (RPE) and preserving outer retinal function (Sakai et al., 2025). Pluripotent stem cell-derived RPE, obtained from embryonic or induced pluripotent stem cells, represents the leading transplantation strategy. These cells can be delivered as suspensions or organized sheets, with the latter offering better structural integration despite greater surgical complexity.

Recent studies demonstrated the feasibility of induced pluripotent stem cell-derived RPE transplantation, with encouraging early safety and anatomical outcomes in patients with macular degeneration (Sakai et al., 2025). However, long-term efficacy remains under investigation.

Major challenges include graft survival, immune compatibility, functional integration, surgical reproducibility, and long-term safety. Although still experimental, cell therapy represents a promising regenerative approach that may complement pharmacological treatment in advanced AMD.

3.7. Innovations in Drug Delivery

Innovative drug-delivery systems aim to prolong therapeutic activity while reducing the need for repeated intravitreal injections (Holekamp et al., 2022; Rodriguez-Cruz et al., 2025).

The most advanced example is the Port Delivery System with ranibizumab, a refillable implant providing continuous intraocular drug release. In the ARCHWAY phase 3 trial, refill every 24 weeks achieved visual outcomes comparable to monthly ranibizumab injections (Holekamp et al., 2022).

Other emerging technologies include biodegradable implants, hydrogels, microneedles, polymeric carriers, and nanotechnology-based platforms designed to improve drug stability, sustained release, and retinal drug delivery (Rodriguez-Cruz et al., 2025). Although most remain in preclinical or early clinical development, they may enhance treatment adherence, reduce healthcare burden, and improve long-term management of AMD. Their widespread implementation, however, depends on confirmation of long-term safety and cost-effectiveness.

3.8. Future Directions: Precision Medicine, Biomarkers, and Artificial Intelligence

Future AMD management is expected to rely increasingly on precision medicine, integrating disease stage, imaging biomarkers, genetic risk, and individualized therapeutic selection (Crincoli et al., 2024; Fleckenstein et al., 2024; Vemulakonda et al., 2025).

Optical coherence tomography (OCT), fundus autofluorescence, OCT angiography, and multimodal imaging already play a central role in monitoring disease progression and treatment response. These technologies generate large datasets that support predictive modeling and personalized treatment planning.

Artificial intelligence (AI) is emerging as a key tool for AMD diagnosis, disease grading, progression prediction, and treatment-response assessment using retinal imaging (Crincoli et al., 2024; Waszak et al., 2025). AI may improve screening, optimize follow-up, and facilitate early identification of high-risk patients.

However, widespread implementation requires external validation, transparency, and integration into clinical decision-making rather than replacement of clinician judgment.

The future of AMD management will likely combine multimodal imaging, biomarkers, AI-assisted risk assessment, mechanism-based therapies, and long-acting drug-delivery systems to provide more personalized and efficient retinal care, particularly in aging populations with increasing demand for ophthalmic services.

4. Discussion

Recent advances in AMD management reflect a shift from symptom control toward mechanism-based, durable, and personalized therapies (Fleckenstein et al., 2024; Guymer & Wu, 2023). Although anti-VEGF therapy remains the standard treatment for neovascular AMD, its long-term effectiveness is limited by repeated injections, undertreatment, and incomplete response in some patients (Fleckenstein et al., 2024; Vemulakonda et al., 2025). Faricimab illustrates the evolution of antiangiogenic therapy by providing comparable efficacy with longer treatment intervals through dual VEGF-A and angiopoietin-2 inhibition (Heier et al., 2022; Khanani, Kotecha, et al., 2024).

Complement inhibitors have transformed the management of geographic atrophy by introducing the first disease-modifying pharmacological therapies. Although they do not restore lost retinal tissue, pegcetacoplan and avacincaptad pegol slow lesion progression and may preserve retinal function for longer (Heier et al., 2023; Khanani et al., 2023). Their long-term value will depend on patient selection, safety, cost-effectiveness, and sustained clinical benefit.

Gene therapy, regenerative medicine, and advanced drug-delivery systems represent promising strategies for reducing treatment burden and improving long-term disease control (Campochiaro et al., 2024; Khanani, Boyer, et al., 2024; Sakai et al., 2025). Likewise, sustained-release technologies, including the Port Delivery System, may improve adherence and reduce demands on healthcare systems (Holekamp et al., 2022; Rodriguez-Cruz et al., 2025).

Artificial intelligence, multimodal imaging, and precision medicine are expected to further optimize AMD management by supporting early diagnosis, progression prediction, individualized treatment, and more efficient use of healthcare resources (Crincoli et al., 2024; Waszak et al., 2025). However, successful implementation requires robust validation, interoperability, clinician oversight, and equitable access.

Future AMD care is likely to combine targeted pharmacological therapies, regenerative medicine, AI-assisted diagnostics, and innovative drug-delivery systems to achieve more durable, personalized, and sustainable treatment.

5. Conclusions

Age-related macular degeneration is a multifactorial retinal disease driven by aging, oxidative stress, inflammation, complement dysregulation, RPE dysfunction, and pathological angiogenesis. Anti-VEGF therapy remains the standard treatment for neovascular AMD, while complement inhibitors have become the first disease-modifying option for geographic atrophy (Heier et al., 2022; Heier et al., 2023; Khanani et al., 2023).

Emerging therapies, including gene therapy, cell-based regeneration, sustained drug-delivery systems, nanotechnology, imaging biomarkers, and AI-assisted precision medicine, have the potential to improve treatment durability, reduce patient burden, and support individualized care. Nevertheless, further high-quality studies are required to establish their long-term safety, effectiveness, accessibility, and cost-effectiveness before widespread clinical implementation.

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