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SELECTED CONTEMPORARY THERAPEUTIC STRATEGIES FOR AGE-RELATED MACULAR DEGENERATION: EFFICACY, SAFETY, AND FUTURE DIRECTIONS

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ABSTRACT

Age-related macular degeneration (AMD) is one of the leading causes of irreversible central vision impairment in older adults. The introduction of intravitreal vascular endothelial growth factor (VEGF) inhibitors has fundamentally changed the prognosis of neovascular AMD (nAMD). Contemporary research focuses both on maintaining functional efficacy while reducing treatment burden and on developing effective therapies for geographic atrophy (GA).

The aim of this review is to critically evaluate selected contemporary therapeutic strategies used or investigated in AMD, with particular emphasis on efficacy, safety, durability of treatment effect, and the quality of available evidence. The evidence evaluated primarily comprised randomized controlled trials, systematic reviews, and meta-analyses, supplemented by early-phase clinical trials for experimental technologies and post-marketing data when relevant safety signals were identified.

The most mature body of evidence demonstrating preservation or improvement of visual function in nAMD concerns anti-VEGF therapy. The PULSAR and TENAYA/LUCERNE trials demonstrated that aflibercept 8 mg and faricimab, respectively, can be administered at extended treatment intervals while maintaining non-inferior functional efficacy compared with active comparators [8–11]. The ranibizumab Port Delivery System (PDS) represents an alternative strategy for reducing the frequency of intravitreal injections but requires surgical implantation [17,18].

In GA, the complement inhibitors pegcetacoplan and avacincaptad pegol have demonstrated modest reductions in the rate of anatomical disease progression [32–34]. These effects should not be interpreted as retinal regeneration or as necessarily translating into improved visual function. For pegcetacoplan, post-marketing safety signals are also clinically relevant [41]. The European Medicines Agency (EMA) did not grant marketing authorization for Syfovre in the European Union, concluding that the demonstrated reduction in GA lesion growth did not translate into a sufficiently meaningful clinical benefit for patients to establish a positive benefit-risk balance [42].

Photobiomodulation demonstrated statistically significant functional outcomes in the LIGHTSITE III program; however, its evidence base remains substantially smaller than that supporting anti-VEGF therapy [35,36]. Gene therapies represent a promising investigational approach, but current evidence is derived predominantly from early-phase studies and is insufficient to establish these treatments as equivalent or superior alternatives to standard anti-VEGF therapy [37,38].

KEYWORDS

Age-related Macular Degeneration, AMD, anti-VEGF, Aflibercept, Faricimab, Pegcetacoplan, Avacincaptad Pegol, Geographic Atrophy, Photobiomodulation, Gene Therapy

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1. Introduction

Age-related macular degeneration is a chronic, progressive disease affecting the central retina, with prevalence increasing substantially with age. Given global population ageing, the epidemiological burden of AMD is expected to continue to increase [1,2].

Two advanced forms of the disease are of particular clinical importance: neovascular AMD and geographic atrophy associated with advanced non-neovascular AMD. The mechanisms responsible for visual function loss, and consequently the therapeutic targets, differ considerably between these phenotypes.

In nAMD, pathological neovascularization and increased vascular permeability lead to exudation, hemorrhage, photoreceptor damage, and ultimately fibrosis. Identification of VEGF as a key mediator of pathological neovascularization led to the development of anti-VEGF therapies, which have become the cornerstone of contemporary nAMD treatment [3–7].

A major challenge, however, remains the considerable treatment burden associated with regular monitoring and repeated intravitreal injections. Consequently, therapeutic development has increasingly focused on strategies that extend treatment intervals, including agents with greater durability, treat-and-extend regimens, sustained drug-delivery systems, and gene therapies.

The therapeutic landscape of GA differs substantially. Loss of retinal pigment epithelium and photoreceptor cells is irreversible; therefore, the primary objective of emerging therapies is to slow further progression of atrophy rather than restore tissue that has already been lost.

The aim of this review is to critically evaluate selected contemporary therapeutic strategies for AMD, with particular emphasis on the quality of available evidence, magnitude of clinical benefit, safety, treatment durability, and potential for reducing treatment burden.

2. Literature Selection Methods

This article was prepared as a narrative review of the literature focused on selected contemporary therapeutic approaches to AMD.

Key publications were identified primarily through searches of PubMed/MEDLINE, with emphasis on randomized controlled trials (RCTs), systematic reviews, and meta-analyses evaluating the interventions discussed. For novel or experimental approaches for which adequately powered late-phase randomized trials were unavailable, early-phase clinical studies were also considered.

Priority was given to human studies with active or sham comparator groups and longer follow-up periods. Older publications were included when they represented landmark studies fundamental to the development of contemporary AMD management, including MARINA, ANCHOR, CATT, VIEW, AREDS, and AREDS2.

Evidence from RCTs was supplemented with post-marketing data when clinically important safety signals emerged that had not been identified or adequately characterized in pivotal clinical trials. EMA documents were used to verify the regulatory status of selected therapies in the European Union.

This article is not a systematic review. No prospectively registered systematic review protocol, complete PRISMA methodology, independent study selection by two reviewers, or formal assessment of the certainty of the overall body of evidence using the GRADE framework was undertaken. The conclusions should therefore be interpreted as a critical narrative synthesis of selected clinical evidence rather than the findings of a formal systematic review.

3. Anti-VEGF Therapy in Neovascular AMD

3.1. Foundations of anti-VEGF therapy

The landmark MARINA and ANCHOR trials demonstrated that ranibizumab could not only reduce the risk of vision loss but also improve visual acuity in a proportion of patients with nAMD [3,4].

The CATT trial demonstrated broadly comparable functional efficacy of ranibizumab and bevacizumab when administered according to analogous treatment regimens [5,6]. The VIEW trials subsequently established the efficacy of aflibercept and further expanded the therapeutic options available for nAMD [7].

The contemporary therapeutic challenge therefore extends beyond achieving biological efficacy alone. An increasingly important objective is to reduce the frequency of injections and clinical visits while maintaining adequate disease control.

3.2. Aflibercept 8 mg

The PULSAR trial compared aflibercept 8 mg administered initially at 12- or 16-week intervals with aflibercept 2 mg administered every 8 weeks after three initial monthly doses.

PULSAR was designed as a randomized, double-masked, phase 3 non-inferiority trial, rather than a superiority trial. At week 48, both aflibercept 8 mg regimens met the prespecified non-inferiority criterion compared with aflibercept 2 mg for change in best-corrected visual acuity (BCVA) [8].

At week 96, mean BCVA changes from baseline were +5.6, +5.5, and +6.6 letters in the aflibercept 8 mg every-12-week, aflibercept 8 mg every-16-week, and aflibercept 2 mg every-8-week groups, respectively. Among patients completing 96 weeks, the mean numbers of active injections were 9.7, 8.2, and 12.8, respectively [9].

These findings require appropriate interpretation because treatment intervals in the 8 mg groups could be modified according to prespecified disease activity criteria. The results therefore do not indicate that every patient can be successfully maintained at the maximum extended interval throughout treatment.

The principal potential clinical advantage of aflibercept 8 mg is therefore a reduction in injection frequency while maintaining functional efficacy, rather than demonstrated superiority over aflibercept 2 mg in terms of BCVA.

3.3. Faricimab

Faricimab is a bispecific antibody that simultaneously targets VEGF-A and angiopoietin-2. Its efficacy and durability were evaluated in the two large randomized, double-masked, phase 3 TENAYA and LUCERNE trials.

Both studies were designed as non-inferiority trials. Faricimab administered at intervals of up to 16 weeks demonstrated non-inferior BCVA outcomes compared with aflibercept administered every 8 weeks [10].

These findings should not be interpreted as evidence that faricimab is superior to aflibercept in improving visual acuity. Their principal clinical relevance lies in the potential for extending treatment intervals in a substantial proportion of appropriately selected patients [10,11].

3.4. Brolucizumab

In the HAWK and HARRIER trials, brolucizumab demonstrated non-inferior functional efficacy compared with aflibercept [12]. Subsequent analyses, however, identified a clinically important safety signal involving intraocular inflammation, retinal vasculitis, and retinal vascular occlusion [13].

Brolucizumab therefore illustrates the importance of assessing potential benefits related to treatment durability in conjunction with therapy-specific safety risks.

3.5. Treat-and-extend regimens

The treat-and-extend (T&E) approach involves individualized extension or shortening of intervals between injections according to disease activity.

Randomized trials and meta-analyses suggest that appropriately implemented T&E regimens can maintain favorable functional outcomes while reducing treatment burden compared with fixed monthly dosing [14–16].

T&E should nevertheless be regarded as an individualized treatment strategy rather than a single standardized dosing schedule.

4. Safety of Intravitreal Anti-VEGF Therapy

Assessment of anti-VEGF safety requires differentiation between complications related to the intravitreal injection procedure itself and adverse events potentially attributable to individual therapeutic agents.

One of the most serious, although uncommon, complications of intravitreal injection is infectious endophthalmitis. A meta-analysis encompassing more than 350,000 anti-VEGF injections reported an incidence of approximately 0.056% per injection [39].

A specific safety concern has emerged for brolucizumab, for which intraocular inflammation, retinal vasculitis, and retinal vascular occlusion have been reported [13].

Regarding systemic safety, a meta-analysis of 74 randomized clinical trials did not demonstrate an overall increase in major adverse cardiovascular events associated with intravitreal anti-VEGF therapy, although safety in selected high-risk patient populations continues to warrant individualized clinical assessment [40].

5. Ranibizumab Port Delivery System

The Port Delivery System is a surgically implanted intraocular drug-delivery device designed to provide continuous release of ranibizumab into the vitreous cavity.

ARCHWAY was a randomized, phase 3, open-label trial with masked visual acuity assessment. The trial was designed to assess non-inferiority and equivalence of PDS with ranibizumab compared with monthly intravitreal ranibizumab [17].

A total of 418 patients were enrolled and randomized in a 3:2 ratio: 251 were assigned to the PDS group and 167 to monthly intravitreal ranibizumab. The primary efficacy endpoint was the change from baseline in BCVA averaged over weeks 36 and 40 [17].

PDS therefore offers the potential to substantially reduce the frequency of conventional intravitreal injections while maintaining functional outcomes in appropriately selected patients. However, this reduction in injection frequency comes with the requirement for surgical implantation and a distinct adverse-event profile associated with both the device and the implantation procedure [17,18].

6. Photodynamic Therapy

Photodynamic therapy (PDT) with verteporfin represented an important therapeutic approach for neovascular AMD before the anti-VEGF era. The TAP trials demonstrated that PDT could reduce vision loss in selected types of choroidal neovascular lesions [19].

Its role in typical nAMD has diminished substantially following the introduction of anti-VEGF agents. However, PDT continues to have a role in selected phenotypes, particularly polypoidal choroidal vasculopathy (PCV).

EVEREST II demonstrated benefits of combining ranibizumab with PDT in PCV [20]. Conversely, the PLANET trial provided evidence supporting the efficacy of aflibercept monotherapy in this population, with relatively few patients requiring rescue PDT [21].

7. Radiotherapy

Radiotherapy has been investigated as a potential strategy to reduce the need for repeated anti-VEGF injections in nAMD.

The randomized, double-masked STAR trial compared stereotactic radiotherapy (SRT) with a sham procedure in patients with chronically active nAMD receiving anti-VEGF treatment [24].

Although initial observations suggested a modest reduction in the number of required injections, long-term follow-up did not demonstrate a favorable overall clinical benefit-risk profile. During years 3 and 4, visual acuity outcomes were less favorable and microvascular abnormalities were more frequent in the SRT group [25].

The available long-term evidence therefore does not support the routine use of stereotactic radiotherapy as standard treatment for nAMD.

8. Laser Photocoagulation

Laser photocoagulation represents a historically important stage in the development of treatment for neovascular AMD. The Macular Photocoagulation Study demonstrated that laser treatment could reduce the risk of severe vision loss in selected neovascular lesions [26].

However, treatment caused irreversible damage to the treated retina and was limited by lesion location. In the anti-VEGF era, conventional laser photocoagulation is no longer routinely used for typical subfoveal nAMD [27].

Laser treatment of drusen has likewise not demonstrated convincing efficacy in preventing progression to advanced AMD [28].

9. AREDS and AREDS2 Supplementation

Nutritional supplementation does not reverse established advanced AMD but can reduce the risk of progression in appropriately selected patients.

The AREDS trial demonstrated a benefit of a specific high-dose combination of antioxidants and zinc in patients with defined categories of AMD severity [29].

AREDS2 evaluated, among other modifications, replacement of beta-carotene with lutein and zeaxanthin and the potential role of omega-3 fatty acids [30]. Long-term AREDS2 analyses support the use of lutein and zeaxanthin instead of beta-carotene, an approach of particular importance from a safety perspective in current and former smokers [31].

10. Complement Inhibition in Geographic Atrophy

10.1. Pegcetacoplan

Pegcetacoplan is an inhibitor of complement component C3. Its efficacy was evaluated in the two randomized, double-masked, sham-controlled phase 3 OAKS and DERBY trials, which enrolled a total of 1,258 patients [32].

At 24 months, pegcetacoplan reduced the rate of GA lesion growth compared with sham treatment. Importantly, this effect primarily concerned anatomical progression of atrophy and should not be interpreted as restoration of damaged retinal tissue or recovery of previously lost visual function [32].

Safety of pegcetacoplan

In OAKS and DERBY, pegcetacoplan treatment was associated with a higher incidence of new-onset neovascular AMD compared with sham treatment [32].

Following the introduction of pegcetacoplan into clinical practice in the United States, an additional post-marketing safety signal of retinal vasculitis emerged. The Research and Safety in Therapeutics (ReST) Committee of the American Society of Retina Specialists confirmed retinal vasculitis in 14 eyes of 13 patients; occlusive retinal vasculopathy was identified in 11 of the 14 affected eyes [41].

These data should not, however, be used to calculate the incidence of this complication in the overall treated population. The ReST analysis represents a retrospective case series of reported events and therefore provides a different level of evidence from prospective randomized controlled trials.

European regulatory status

Pegcetacoplan did not receive marketing authorization in the European Union for the treatment of GA. Following re-examination, the Committee for Medicinal Products for Human Use confirmed its recommendation to refuse marketing authorization on September 19, 2024. The EMA concluded that although the medicine reduced the rate of GA lesion growth, a sufficiently meaningful benefit in patients' everyday functioning had not been demonstrated to establish a positive benefit-risk balance [42].

10.2. Avacincaptad pegol

Avacincaptad pegol is an inhibitor of complement component C5. In the phase 3 GATHER2 trial, treatment reduced the rate of GA lesion growth compared with sham treatment [33].

Two-year results published subsequently provided additional evidence regarding the efficacy and safety of treatment [34]. Importantly, GATHER2 enrolled patients with non-center-point-involving GA, which should be considered when generalizing the findings to the broader GA population.

As with pegcetacoplan, the demonstrated treatment effect primarily represents slowing of anatomical disease progression rather than regeneration of previously lost retinal tissue.

Avacincaptad pegol does not currently have marketing authorization in the European Union for this indication. Astellas Pharma Europe B.V. withdrew its marketing authorization application for Izelvay on October 24, 2024. According to the EMA, the company stated that the withdrawal was based on concerns raised by the Agency regarding the medicine's efficacy. Withdrawal of an application is not equivalent to a formal refusal of marketing authorization [43].

11. Photobiomodulation

Photobiomodulation (PBM) uses light at selected wavelengths with the aim of modulating cellular and mitochondrial processes.

The LIGHTSITE III program evaluated PBM in patients with non-exudative AMD. In the long-term 24-month analysis, the study met its prespecified BCVA endpoint, with a statistically significant difference reported in favor of PBM [36].

These findings nevertheless require cautious interpretation. The evidence base for PBM remains considerably smaller than that comprising the numerous independent RCTs and meta-analyses supporting anti-VEGF therapy. Positive findings from a single clinical development program should not automatically be interpreted as providing an equivalent level of evidence.

12. Gene Therapy

Gene therapy represents one of the most promising investigational strategies aimed at achieving sustained intraocular production of therapeutic proteins that inhibit VEGF.

However, the developmental stage of these technologies should be clearly distinguished from the maturity of evidence supporting established anti-VEGF treatments. Phase 1 and phase 1/2 studies are primarily designed to assess safety, tolerability, dose selection, and signals of biological activity rather than to demonstrate comparative clinical efficacy.

12.1. RGX-314

An open-label, phase 1/2a dose-escalation study evaluated subretinal administration of RGX-314. A total of 42 patients received treatment across five dose cohorts [37].

Sustained expression of the therapeutic protein and reductions in the requirement for supplemental anti-VEGF injections were observed in selected cohorts.

However, given the small study population, open-label design, absence of a randomized active comparator, and early phase of development, these findings should primarily be interpreted as evidence of biological activity and potential durability. They do not demonstrate superiority or equivalence of RGX-314 compared with contemporary standard anti-VEGF therapy.

12.2. Ixoberogene soroparvovec

The OPTIC trial evaluated a single intravitreal administration of ixoberogene soroparvovec, a gene therapy designed to encode aflibercept. OPTIC was a prospective, open-label, multicenter phase 1 study in which the primary objective was safety assessment [38].

The observed reduction in the need for supplemental anti-VEGF treatment represents an encouraging signal. However, given the early phase of the study, lack of a randomized comparator, and limited sample size, these findings do not establish comparative efficacy.

13. Comparison of Selected Therapeutic Strategies

Strategy	AMD phenotype	Principal outcome	Key conclusion from the evidence discussed
Established anti-VEGF agents	nAMD	BCVA	Multiple RCTs demonstrate preservation and, in some patients, improvement of BCVA
Aflibercept 8 mg	nAMD	BCVA/treatment interval	Non-inferior to aflibercept 2 mg with the potential for extended dosing intervals
Faricimab	nAMD	BCVA/treatment interval	Non-inferior to aflibercept with extended treatment intervals possible in a proportion of patients
Brolucizumab	nAMD	BCVA/anatomical outcomes	Functional efficacy accompanied by a clinically important therapy-specific safety signal
Treat-and-extend	nAMD	BCVA/treatment burden	Individualized treatment can reduce treatment burden while maintaining favorable functional outcomes
PDS	nAMD	BCVA/treatment burden	Non-inferiority/equivalence with reduced conventional injection frequency but a distinct procedural safety profile
PDT	nAMD/PCV	BCVA/anatomical outcomes	Limited role in typical nAMD; remains relevant in selected PCV phenotypes
SRT	nAMD	Injection burden/BCVA	Long-term evidence does not support routine use
AREDS2	Non-neovascular AMD	AMD progression	Reduces progression risk in appropriately selected patients; does not treat established GA
Pegcetacoplan	GA	GA lesion growth	Slows anatomical progression without restoring lost retinal tissue
Avacincaptad pegol	GA	GA lesion growth	Modestly slows anatomical progression
PBM	Non-exudative AMD	BCVA	Positive LIGHTSITE III findings, but the independent evidence base remains limited
Gene therapy	nAMD	Safety/treatment burden	Promising early-phase signals; comparative efficacy remains unproven

14. Discussion

The evolution of AMD treatment demonstrates that the concept of therapeutic “efficacy” cannot be reduced to a single universal endpoint.

In nAMD, preservation or improvement of visual function remains the most clinically meaningful therapeutic outcome. Multiple randomized trials of anti-VEGF therapy have demonstrated such effects, making this therapeutic class the one supported by the most mature body of evidence [3–13].

A major focus of more recent development is no longer simply to achieve greater improvements in BCVA, but to increase treatment durability. PULSAR and TENAYA/LUCERNE demonstrate that treatment intervals can be extended in a proportion of patients while maintaining functional efficacy [8–11].

These findings require an appropriate understanding of non-inferiority trial methodology. Demonstrating non-inferiority does not establish superiority of a new treatment over its comparator.

Even greater caution is required when interpreting therapeutic effects in GA. Pegcetacoplan and avacincaptad pegol reduce the rate of growth of atrophic lesions, but an anatomical treatment effect is not equivalent to improved visual function [32–34]. The EMA assessment of Syfovre further emphasizes the importance of distinguishing a statistically significant effect on an anatomical endpoint from a clinically meaningful benefit in patients' daily functioning [42].

Safety findings also illustrate the limitations of relying exclusively on pivotal clinical trials. Rare adverse events may become apparent only after a therapy is administered to substantially larger populations in routine clinical practice. Post-marketing reports of retinal vasculitis following pegcetacoplan treatment illustrate the importance of pharmacovigilance in comprehensive benefit-risk assessment [41].

PBM and gene therapy represent different stages of therapeutic development. LIGHTSITE III provides randomized evidence suggesting a functional benefit of PBM, although the independent evidence base remains limited [35,36]. Gene therapies may potentially transform the treatment model by providing sustained production of a therapeutic protein following a single administration; however, available clinical data are not yet sufficient to place these approaches on an equivalent evidentiary footing with established anti-VEGF therapy [37,38].

15. Limitations

This article is a narrative review and therefore has limitations inherent to this type of publication.

No prospectively registered systematic review protocol, complete PRISMA methodology, independent study selection by two reviewers, or formal GRADE assessment of the certainty of the overall body of evidence was undertaken. Selection bias in the choice of included publications therefore cannot be excluded.

Publication bias may also influence the available evidence, particularly in therapeutic areas supported by relatively few studies or predominantly early-phase clinical trials.

Direct comparisons among individual therapies are complicated by heterogeneity in study populations, eligibility criteria, dosing regimens, follow-up duration, and outcome measures. Changes in BCVA, GA lesion growth, and the number of required injections represent different dimensions of therapeutic effect and should not be regarded as interchangeable measures of efficacy.

The predominance of randomized clinical trial evidence strengthens the internal validity of conclusions regarding efficacy under controlled conditions but may limit full generalizability to routine clinical practice, where adherence, visit frequency, comorbidities, and treatment burden can influence real-world outcomes.

A substantial proportion of pivotal trials evaluating newer therapies were industry sponsored. Industry funding does not itself invalidate study findings; however, funding sources should be considered during critical interpretation, particularly when evaluating exploratory and post hoc analyses.

For gene therapies, available evidence is derived predominantly from small early-phase studies, while the number of large independent trials evaluating PBM remains limited.

Finally, the safety profile of new therapies may not be fully characterized before their use in larger patient populations. Post-marketing pharmacovigilance therefore provides an important complement to randomized clinical trials in identifying rare adverse events.

16. Conclusions

The largest and most mature body of high-quality randomized evidence supporting preservation or improvement of visual function in neovascular AMD concerns intravitreal anti-VEGF therapy.

Development within this therapeutic class increasingly focuses on maintaining efficacy while reducing treatment burden. Faricimab and aflibercept 8 mg met prespecified non-inferiority criteria against active comparators in their respective pivotal trials while allowing extended treatment intervals in a proportion of patients [8–11].

Treatment assessment must also incorporate safety. Clinically relevant concerns include retinal vasculitis and retinal vascular occlusion associated with brolucizumab and the distinct procedure- and device-related adverse-event profile associated with surgically implanted PDS [13,17,18].

In GA, pegcetacoplan and avacincaptad pegol have demonstrated modest slowing of anatomical disease progression [32–34]. These effects should not be interpreted as regeneration of lost retinal tissue or as necessarily translating into improved visual function. For pegcetacoplan, post-marketing retinal vasculitis and the EMA's negative benefit-risk assessment for the proposed indication must also be considered [41,42].

PBM demonstrated a positive functional outcome in LIGHTSITE III but requires further independent validation [35,36]. Gene therapies remain investigational, and the available evidence is currently insufficient to establish them as equivalent or superior alternatives to standard anti-VEGF therapy [37,38].

Ultimately, evaluation of emerging AMD therapies should integrate the magnitude of treatment effect, nature of the primary endpoint, impact on visual function, short- and long-term safety, treatment burden, and clinical relevance of the benefit to the patient. A statistically significant change in an anatomical parameter or a reduction in the number of treatment procedures should not, in isolation, be equated with clinical superiority.

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