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Long-term Visual Outcomes Following Anti-VEGF Therapy for Neovascular Age-related Macular Degeneration

Abstract
Neovascular age-related macular degeneration (nAMD) remains the leading cause of irreversible central vision loss among older adults in developed countries. The introduction of intravitreal vascular endothelial growth factor (VEGF) inhibitors has revolutionized disease management, transforming nAMD from a rapidly blinding condition into a chronic, treatable disorder. Landmark randomized clinical trials demonstrated substantial improvements in visual acuity during the first two years of treatment; however, maintaining these gains over longer follow-up periods remains a significant clinical challenge. Long-term visual outcomes are influenced by multiple factors, including treatment regimen, injection frequency, baseline visual acuity, lesion characteristics, patient adherence, and the progressive development of macular atrophy and subretinal fibrosis. Furthermore, discrepancies between randomized clinical trials and real-world practice highlight the impact of undertreatment and healthcare resource limitations on long-term visual preservation. Recent therapeutic advances, including faricimab, high-dose aflibercept, sustained drug-delivery systems, gene therapy, and artificial intelligence-assisted treatment strategies, offer promising opportunities to reduce treatment burden while maintaining visual outcomes. This review critically evaluates evidence from landmark clinical trials, extension studies, and real-world registries regarding long-term visual outcomes following anti-VEGF therapy for nAMD. Particular emphasis is placed on determinants of long-term visual prognosis, current therapeutic challenges, emerging treatment strategies, and practical recommendations for optimizing lifelong management.

1. INTRODUCTION

Age-related macular degeneration (AMD) is a progressive degenerative disorder of the macula and represents one of the leading causes of irreversible visual impairment among individuals aged 50 years and older worldwide. With continued population aging, the global prevalence of AMD is expected to increase substantially over the coming decades, posing an increasing socioeconomic and healthcare burden. Although neovascular AMD (nAMD) accounts for only approximately 10–15% of all AMD cases, it is responsible for nearly 90% of severe central vision loss associated with the disease because of the rapid development of choroidal neovascularization (CNV), exudation, hemorrhage, and subsequent fibrotic scarring if left untreated [1–3].

The pathogenesis of nAMD is multifactorial and involves a complex interaction between aging, oxidative stress, chronic inflammation, complement pathway dysregulation, genetic susceptibility, and retinal pigment epithelium (RPE) dysfunction. These mechanisms ultimately promote excessive expression of vascular endothelial growth factor (VEGF), a potent angiogenic cytokine that stimulates abnormal choroidal neovascularization, increases vascular permeability, and promotes leakage of plasma and blood beneath and within the neurosensory retina. Persistent VEGF-mediated exudation results in photoreceptor damage, disruption of retinal architecture, fibrosis, and irreversible vision loss if disease activity is not adequately controlled [4,5].

The introduction of intravitreal anti-VEGF therapy fundamentally transformed the management of nAMD. Before anti-VEGF agents became available, treatment options such as thermal laser photocoagulation and photodynamic therapy were primarily aimed at slowing disease progression rather than improving vision, and long-term visual prognosis remained poor. The development of ranibizumab, followed by bevacizumab, aflibercept, brolucizumab, and more recently faricimab, shifted the treatment paradigm from preventing blindness to preserving and, in many patients, improving visual acuity [6–8].

Landmark randomized controlled trials—including MARINA, ANCHOR, CATT, IVAN, VIEW 1, VIEW 2, and HARBOR—consistently demonstrated that regular intravitreal anti-VEGF therapy can produce significant improvements in best-corrected visual acuity (BCVA) during the first one to two years of treatment, with many patients gaining ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters [9–15]. These studies established anti-VEGF therapy as the international standard of care for nAMD and fundamentally altered expectations regarding disease prognosis.

Despite these remarkable short-term results, maintaining visual gains over extended follow-up remains considerably more challenging. Long-term extension studies and large real-world registries have demonstrated that many patients experience gradual visual decline after the initial treatment years, even with ongoing anti-VEGF therapy. This deterioration is multifactorial and reflects progressive retinal degeneration, development of macular atrophy and subretinal fibrosis, treatment burden, reduced injection frequency, undertreatment, and declining patient adherence over time [16–19]. Consequently, visual outcomes reported in routine clinical practice often differ substantially from those achieved in randomized clinical trials, emphasizing the importance of evaluating long-term effectiveness beyond controlled research settings.

Over the past decade, management strategies have evolved from fixed monthly dosing to individualized treatment approaches such as pro re nata (PRN) and treat-and-extend (T&E) regimens, aiming to balance visual outcomes with treatment burden. Simultaneously, newer therapeutic agents with extended durability, dual-pathway inhibition, sustained drug-delivery systems, and gene therapy are being developed to reduce injection frequency while preserving visual function [20–23]. These advances have shifted attention from simply achieving early visual improvement toward maintaining functional vision throughout the patient's lifetime.

Given the chronic nature of nAMD, evaluating long-term visual outcomes has become increasingly important for clinicians, researchers, and healthcare systems. Understanding why some patients maintain excellent vision for a decade whereas others experience progressive visual deterioration despite treatment is essential for optimizing individualized management strategies, improving adherence, minimizing irreversible retinal damage, and guiding future therapeutic innovation.

Therefore, this comprehensive review critically examines the current evidence regarding long-term visual outcomes following anti-VEGF therapy for nAMD. Particular emphasis is placed on evidence from landmark randomized clinical trials, long-term extension studies, and real-world registries, together with factors influencing visual prognosis, current therapeutic challenges, emerging treatment strategies, and practical recommendations for optimizing long-term patient care.

2. LONG-TERM VISUAL OUTCOMES FOLLOWING ANTI-VEGF THERAPY

The introduction of intravitreal anti-VEGF therapy fundamentally changed the natural history of neovascular age-related macular degeneration (nAMD). Before its introduction, most patients experienced progressive and irreversible central vision loss despite available treatments, including thermal laser photocoagulation and photodynamic therapy. Anti-VEGF therapy not only slowed disease progression but also became the first intervention capable of producing clinically meaningful improvements in visual acuity. However, although early outcomes have been consistently excellent, maintaining these gains over prolonged follow-up remains considerably more challenging. Consequently, evaluation of long-term visual outcomes has become increasingly important for determining the true effectiveness of anti-VEGF therapy in routine clinical practice.

Evidence regarding long-term outcomes originates from three principal sources: landmark randomized controlled trials (RCTs), long-term extension studies, and real-world observational registries. Randomized trials provide high-quality evidence regarding efficacy under controlled conditions, whereas real-world studies reflect everyday clinical practice, where treatment adherence, healthcare accessibility, and individualized management substantially influence outcomes. Together, these complementary sources provide a comprehensive

understanding of visual prognosis throughout the disease course.

Landmark Randomized Clinical Trials

The modern era of nAMD treatment began with the publication of the MARINA and ANCHOR trials, which established ranibizumab as the first anti-VEGF agent capable of significantly improving visual acuity rather than simply slowing visual deterioration. Both studies demonstrated that monthly ranibizumab injections produced sustained visual improvement over two years, with approximately one-third of treated patients achieving gains of at least 15 ETDRS letters while over 90% avoided moderate vision loss [9,10]. These results represented an unprecedented improvement compared with previous treatment modalities and established monthly anti-VEGF therapy as the international standard of care.

Subsequent comparative effectiveness studies further refined treatment strategies. The Comparison of Age-related Macular Degeneration Treatments Trials (CATT) demonstrated that bevacizumab and ranibizumab achieved comparable visual outcomes when administered according to similar treatment regimens, providing important evidence supporting the widespread clinical use of bevacizumab because of its substantially lower cost [11]. Likewise, the IVANtrial confirmed similar efficacy between the two agents while also examining continuous versus discontinuous treatment strategies, emphasizing the importance of maintaining adequate treatment intensity to preserve visual gains [12].

The introduction of aflibercept further expanded therapeutic options. The VIEW 1 and VIEW 2 studies demonstrated that aflibercept administered every eight weeks after three initial monthly injections achieved visual outcomes comparable to monthly ranibizumab while reducing injection frequency [13]. This finding represented a major advance in reducing treatment burden without compromising efficacy and influenced treatment protocols worldwide.

The HARBOR study subsequently evaluated different ranibizumab doses and individualized treatment regimens. Although higher dosing did not significantly improve visual outcomes, individualized treatment approaches demonstrated that many patients could maintain favorable visual acuity with fewer injections when disease activity was carefully monitored [14]. Collectively, these pivotal trials established anti-VEGF therapy as the cornerstone of nAMD management and demonstrated that visual improvement is achievable in a substantial proportion of patients during the first two years of treatment.

The principal characteristics and outcomes of these landmark trials are summarized in Table 1.

Table 1. Landmark Randomized Clinical Trials Evaluating Anti-VEGF Therapy in Neovascular AMD

Trial	Anti-VEGF agent	Follow-up	Main findings	Clinical significance
MARINA	Ranibizumab	24 months	Significant BCVA improvement with monthly treatment	First trial demonstrating visual improvement
ANCHOR	Ranibizumab	24 months	Superior vision gain compared with photodynamic therapy	Established ranibizumab as standard therapy
CATT	Ranibizumab vs bevacizumab	24 months	Comparable efficacy between agents	Supported use of bevacizumab
IVAN	Ranibizumab vs bevacizumab	24 months	Similar long-term efficacy and safety	Reinforced treatment equivalence
VIEW 1 & VIEW 2	Aflibercept	96 weeks	Comparable efficacy with extended dosing intervals	Reduced treatment burden
HARBOR	Ranibizumab	24 months	Individualized regimens maintained visual gains	Supported personalized treatment

Long-Term Extension Studies

Although randomized trials established the efficacy of anti-VEGF therapy during the first two years, extension studies demonstrated that preserving these gains over longer periods is substantially more difficult. The SEVEN-UP study, which followed patients previously enrolled in MARINA, ANCHOR, and HORIZON, reported that visual acuity declined during prolonged follow-up despite continued anti-VEGF treatment. Seven years after initiation of therapy, only a minority of eyes maintained visual acuity of 20/40 or better, while nearly one-third developed visual acuity of 20/200 or worse [15].

Importantly, this deterioration did not necessarily reflect treatment failure but rather the chronic progressive nature of nAMD. Development of geographic atrophy, subretinal fibrosis, chronic photoreceptor damage, and reduced treatment frequency were identified as major contributors to long-term visual decline. These findings shifted clinical focus from achieving short-term visual gains toward maintaining retinal integrity over many years.

Subsequent long-term cohort studies confirmed similar trends. Although many patients retained visual acuity superior to baseline after five years, gradual decline became increasingly evident beyond seven years, particularly among individuals receiving fewer injections or experiencing prolonged treatment interruptions. These

observations emphasized that anti-VEGF therapy suppresses disease activity but does not eliminate the underlying degenerative processes responsible for progressive retinal dysfunction.

Real-World Evidence

While randomized trials remain the gold standard for evaluating efficacy, real-world studies provide essential information regarding effectiveness under routine clinical conditions. Compared with clinical trials, patients in routine practice are generally older, have more systemic comorbidities, exhibit greater disease heterogeneity, and frequently receive fewer injections because of healthcare limitations, financial constraints, or treatment fatigue. Consequently, long-term visual outcomes reported in observational studies are often less favorable than those achieved in randomized trials.

Large observational registries, including the Fight Retinal Blindness! (FRB!) Registry, the LUMINOUS study, and several national cohort studies, consistently demonstrate that visual acuity improves during the first one to two treatment years before gradually declining thereafter [16–18]. Nevertheless, vision generally remains superior to the expected natural history of untreated disease, confirming the long-term benefit of continued anti-VEGF therapy.

One of the most influential long-term registry analyses reported ten-year outcomes from the FRB! Registry, demonstrating that patients receiving more intensive treatment maintained significantly better visual acuity than those treated less frequently. Eyes completing ten years of follow-up experienced only minimal average visual loss from baseline when injection frequency remained relatively high, whereas undertreated patients exhibited substantially greater deterioration. These findings reinforce the importance of maintaining consistent disease suppression throughout long-term follow-up [18].

Similarly, real-world studies have demonstrated that treatment adherence strongly influences visual prognosis. Patients who discontinue treatment prematurely or experience prolonged gaps between visits are more likely to develop irreversible macular fibrosis, geographic atrophy, and permanent vision loss. Therefore, long-term success depends not only on drug efficacy but also on sustained patient engagement and regular monitoring.

Comparison Between Randomized Trials and Real-World Outcomes

A consistent observation across the literature is the disparity between randomized clinical trials and routine clinical practice. Whereas clinical trials typically employ fixed treatment schedules with rigorous follow-up and strict retreatment criteria, real-world practice often involves individualized regimens influenced by healthcare resources, patient compliance, and physician preference.

This difference results in fewer injections and less frequent monitoring in routine practice, which partially explains the smaller visual gains and greater long-term decline observed in observational cohorts. Nevertheless, studies adopting proactive treat-and-extend (T&E) protocols have demonstrated outcomes approaching those reported in randomized trials while substantially reducing treatment burden compared with fixed monthly dosing. These findings suggest that individualized proactive treatment strategies may represent the optimal balance between efficacy and feasibility in contemporary clinical practice.

Overall, current evidence demonstrates that anti-VEGF therapy provides durable visual benefit compared with the natural course of nAMD; however, maintaining early visual gains requires sustained treatment, careful monitoring, and individualized management over many years. The variability observed across long-term studies further indicates that visual prognosis is determined not only by therapeutic efficacy but also by patient characteristics, disease progression, and healthcare delivery systems.

The principal long-term visual outcomes reported by major clinical trials and observational studies are summarized in Table 2.

Table 2. Long-Term Visual Outcomes Following Anti-VEGF Therapy in Major Clinical Studies

Study	Follow-up	Mean visual outcome	Key observations
MARINA	2 years	Significant BCVA improvement	Monthly ranibizumab highly effective
ANCHOR	2 years	Sustained visual gain	Superior to photodynamic therapy
CATT	5 years	Partial loss of early gains	Undertreatment influenced long-term vision
SEVEN-UP	~7 years	Progressive decline from peak BCVA	Atrophy and fibrosis became major determinants
VIEW extension	4–5 years	Stable vision with individualized treatment	Durable aflibercept efficacy
Fight Retinal Blindness! Registry	10 years	Better outcomes with higher injection frequency	Long-term adherence predicted visual preservation
LUMINOUS Registry	5 years	Functional vision maintained in many patients	Real-world treatment burden influenced outcomes

3. FACTORS INFLUENCING LONG-TERM VISUAL OUTCOMES

Although anti-VEGF therapy has transformed the management of neovascular age-related macular degeneration (nAMD), considerable variability exists in

long-term visual outcomes among treated patients. While some individuals maintain functional vision for more than a decade, others experience progressive visual deterioration despite regular treatment. This variability reflects the complex interaction between patient characteristics, disease severity, retinal structural changes, treatment strategy, and healthcare-related factors. Understanding these determinants is essential for optimizing individualized management and maximizing long-term visual preservation.

Baseline Visual Acuity

Baseline best-corrected visual acuity (BCVA) is one of the strongest predictors of long-term visual outcomes. Patients presenting with better baseline vision generally maintain superior final visual acuity after prolonged treatment because retinal architecture is relatively preserved before irreversible photoreceptor damage occurs. Conversely, eyes with poor baseline vision frequently demonstrate larger numerical improvements in ETDRS letter scores but rarely achieve the same absolute visual acuity as patients treated earlier in the disease course [24,25].

This apparent paradox reflects a well-recognized "ceiling effect." Patients with excellent baseline vision have limited opportunity for substantial letter gain but are more likely to preserve functional vision over many years. Consequently, early diagnosis and prompt initiation of therapy remain among the most important determinants of favorable long-term outcomes.

Treatment Intensity and Injection Frequency

Long-term visual preservation is closely associated with adequate treatment intensity. Across randomized clinical trials and real-world registries, patients receiving a greater number of anti-VEGF injections generally maintain better visual acuity than those treated less frequently [18,26].

Undertreatment remains one of the principal causes of long-term visual decline in routine practice. Although exudation may initially resolve after a limited number of injections, recurrent disease activity results in cumulative retinal injury that cannot be completely reversed by subsequent therapy. Each episode of recurrent fluid may contribute to irreversible photoreceptor loss, retinal pigment epithelium dysfunction, and fibrotic remodeling. Evidence from long-term observational studies consistently demonstrates that maintaining disease suppression through proactive retreatment preserves vision more effectively than intermittent reactive treatment after recurrence has already occurred.

Treatment Regimen

The optimal treatment regimen remains an area of ongoing investigation. Three principal strategies are currently employed:

- Fixed dosing
- Pro re nata (PRN)
- Treat-and-Extend (T&E)

Fixed monthly treatment achieved the best visual outcomes in pivotal randomized trials but imposes substantial treatment burden on patients and healthcare systems. Consequently, fixed dosing is seldom maintained beyond the first treatment years in routine clinical practice.

PRN regimens reduce injection frequency by administering treatment only when disease activity recurs. Although this strategy decreases treatment burden, several long-term studies have demonstrated inferior visual outcomes compared with proactive approaches because recurrent exudation often precedes retreatment [27].

Treat-and-Extend protocols have become increasingly popular because they individualize treatment intervals according to disease activity while maintaining continuous suppression of neovascularization. Numerous comparative studies have shown that T&E achieves visual outcomes approaching monthly treatment while substantially reducing clinic visits and unnecessary injections [28]. Accordingly, current international guidelines increasingly recommend T&E as the preferred long-term management strategy for many patients with nAMD.

Anatomical Biomarkers on Optical Coherence Tomography

Optical coherence tomography (OCT) has become indispensable for predicting long-term prognosis and guiding treatment decisions. Structural retinal biomarkers often provide more accurate prognostic information than visual acuity alone because they directly reflect retinal integrity.

Persistent or recurrent intraretinal fluid (IRF) is consistently associated with poorer long-term visual outcomes because it reflects ongoing retinal injury and neuronal damage [29]. In contrast, the prognostic significance of subretinal fluid (SRF) is more controversial. Several studies suggest that small amounts of stable SRF may be compatible with satisfactory visual outcomes and may not require aggressive retreatment, whereas persistent IRF almost invariably warrants continued therapy.

These structural abnormalities indicate irreversible retinal degeneration and frequently predict declining visual function despite successful control of exudation.

Macular Atrophy and Subretinal Fibrosis

As anti-VEGF therapy has prolonged patient survival and disease control, chronic retinal degeneration has become an increasingly important determinant of long-term vision. Macular atrophy and subretinal fibrosis now represent the principal causes of late visual deterioration in many patients receiving prolonged anti-VEGF therapy [30].

Macular atrophy develops through progressive degeneration of the retinal pigment epithelium, photoreceptors, and choriocapillaris. Although its precise relationship with anti-VEGF therapy remains debated, increasing evidence suggests that disease progression itself plays a major role, with cumulative retinal injury, chronic inflammation, and aging contributing substantially to tissue loss.

Subretinal fibrosis similarly results from chronic neovascular activity and wound-healing responses. Once established, fibrotic scars permanently disrupt retinal architecture and are associated with irreversible central vision loss. Importantly, neither macular atrophy nor fibrosis can currently be reversed, highlighting the importance of early disease control and continuous suppression of neovascular activity.

Patient Adherence and Persistence

Long-term success depends not only on treatment efficacy but also on sustained patient adherence. Anti-VEGF therapy often requires repeated injections over many years, creating significant physical, psychological, financial, and logistical challenges for patients and caregivers.

Loss to follow-up, missed appointments, delayed retreatment, and premature treatment discontinuation are consistently associated with poorer visual outcomes [31]. Patients experiencing prolonged interruption of therapy frequently develop recurrent exudation and irreversible retinal damage before treatment can be reinitiated.

Improving adherence therefore represents a major priority in long-term nAMD management. Patient education, individualized scheduling, simplified treatment regimens, and reduction of treatment burden through longer-acting therapies may substantially improve persistence with treatment.

Systemic and Demographic Factors

Several patient characteristics influence long-term prognosis. Increasing age has been associated with less favorable visual outcomes, partly because of reduced retinal regenerative capacity and greater prevalence of systemic comorbidities. Cardiovascular disease, smoking history, and poor general health may also adversely affect retinal function and treatment response.

Genetic factors, particularly polymorphisms involving complement factor H (CFH) and ARMS2/HTRA1, have been investigated extensively; however, their influence on long-term anti-VEGF response remains inconsistent and has not yet altered routine clinical practice.

Anti-VEGF Agent Selection and Switching

Although ranibizumab, bevacizumab, aflibercept, and faricimab demonstrate broadly comparable efficacy in many clinical settings, switching between agents may improve anatomical outcomes in selected patients with persistent disease activity.

Aflibercept has demonstrated superior drying capacity in some eyes with refractory fluid because of its higher VEGF-binding affinity, while faricimab offers additional inhibition of angiopoietin-2, potentially allowing longer treatment intervals without compromising efficacy [32]. Nevertheless, current evidence suggests that treatment adherence and disease monitoring exert greater influence on long-term vision than selection of any individual anti-VEGF agent.

The principal determinants of long-term visual outcomes are summarized in Table 3.

Table 3. Predictors of Favorable and Poor Long-Term Visual Outcomes Following Anti-VEGF Therapy

Factor	Favorable outcome	Poor outcome
Baseline BCVA	Good initial vision	Advanced vision loss at presentation
Treatment timing	Early diagnosis	Delayed treatment initiation
Injection frequency	Regular proactive therapy	Undertreatment
Treatment regimen	Treat-and-Extend or fixed	Inconsistent PRN with prolonged recurrence
OCT findings	Dry macula, preserved ellipsoid zone	Persistent IRF, outer retinal disruption
Macular atrophy	Minimal progression	Extensive geographic atrophy
Fibrosis	Absent	Established subretinal fibrosis
Patient adherence	High compliance	Missed visits and treatment discontinuation
Follow-up	Continuous monitoring	Loss to follow-up
Disease activity	Well-controlled CNV	Recurrent exudation

Collectively, these findings indicate that long-term visual outcomes depend not only on the pharmacological efficacy of anti-VEGF agents but also on early diagnosis, proactive treatment strategies, preservation of retinal structure, and sustained patient adherence. Recognition of these determinants enables clinicians to identify patients at increased risk of visual decline and implement individualized management strategies aimed at maximizing long-term visual preservation.

4. CURRENT CHALLENGES IN LONG-TERM ANTI-VEGF THERAPY

Despite the profound benefits of anti-VEGF therapy for neovascular age-related macular degeneration (nAMD), maintaining favorable visual outcomes over many years remains difficult. Long-term studies demonstrate that visual decline is often related less to loss of pharmacological efficacy than to treatment burden, undertreatment, interruptions in follow-up, and irreversible structural changes such as macular atrophy and subretinal fibrosis [18,33]. These factors contribute substantially to the gap between outcomes achieved in randomized clinical trials and those observed in routine practice.

Treatment Burden and Undertreatment

Repeated intravitreal injections and frequent optical coherence tomography (OCT) monitoring impose considerable burdens on elderly patients, caregivers, clinicians, and healthcare systems. Transportation difficulties, systemic comorbidities, injection-related anxiety, caregiver dependence, and frequent clinic visits may progressively reduce treatment persistence. Consequently, real-world patients generally receive fewer injections than participants in randomized clinical trials, and lower treatment intensity is consistently associated with inferior visual outcomes [33,34].

The five-year CATT follow-up demonstrated partial loss of the early visual gains achieved during the randomized treatment phase, while fewer injections and persistent disease activity were associated with greater risk of sustained visual loss [33,34]. These observations emphasize that nAMD is a chronic disease requiring

prolonged suppression of neovascular activity rather than episodic treatment of symptomatic recurrences.

Proactive Treat-and-Extend strategies can reduce unnecessary visits while maintaining disease control and therefore offer a practical compromise between fixed frequent dosing and reactive PRN treatment. Nevertheless, undertreatment remains an important problem in routine care, particularly where healthcare capacity or patient access is limited.

Loss to Follow-Up and Treatment Discontinuation

Loss to follow-up represents a major modifiable cause of poor long-term visual outcome. Patients may interrupt therapy because of advanced age, illness, transportation difficulties, financial barriers, treatment fatigue, or perceived lack of benefit. Importantly, visual deterioration occurring during prolonged treatment interruption is frequently irreversible despite subsequent resumption of anti-VEGF therapy.

Recent long-term evidence demonstrates significantly worse final visual acuity and a greater risk of severe vision loss among nAMD patients lost to follow-up for more than six months compared with patients maintaining continuous follow-up [35]. Maintaining treatment persistence should therefore be regarded as a core component of nAMD management rather than an administrative consideration alone.

Patient education, reminder systems, coordinated appointment scheduling, caregiver involvement, individualized treatment intervals, and newer longer-duration therapies may reduce the risk of treatment discontinuation.

Macular Atrophy

Macular atrophy has emerged as one of the principal causes of late visual decline among patients whose neovascular activity is otherwise successfully controlled. Progressive loss of the retinal pigment epithelium, photoreceptors, and choriocapillaris can lead to irreversible central visual impairment despite a relatively dry macula on OCT.

Long-term observational studies demonstrate greater rates of visual decline in eyes developing macular atrophy compared with eyes without atrophic progression [36]. However, the relationship between anti-VEGF exposure and atrophy remains complex. Increased treatment intensity has been associated with a higher frequency of macular atrophy in some studies, but chronic nAMD itself, aging, baseline lesion characteristics, and repeated exudative injury are also major contributors [33,36].

Accordingly, undertreatment should not be justified by concern regarding atrophy. The immediate risk of irreversible damage from uncontrolled neovascular activity generally outweighs the uncertain contribution of VEGF suppression to atrophic progression.

Subretinal Fibrosis

Subretinal fibrosis represents another major structural cause of permanent long-term visual impairment. Chronic neovascular activity promotes fibrovascular remodeling and scar formation beneath the neurosensory retina, resulting in irreversible disruption of photoreceptor architecture.

Fibrosis is particularly associated with delayed treatment initiation, large lesions, recurrent hemorrhage, and persistent disease activity. Once central fibrosis develops, further anti-VEGF therapy may suppress exudation but cannot restore the damaged retinal architecture. Prevention through early diagnosis and sustained control of neovascular activity therefore remains critical.

The increasing contribution of both fibrosis and macular atrophy to late visual loss highlights an important conceptual shift in nAMD management: successful long-term treatment requires preservation of retinal structure, not merely elimination of retinal fluid.

Incomplete Response, Resistance, and Switching Therapy

A proportion of patients demonstrate persistent or recurrent fluid despite apparently adequate anti-VEGF therapy. Potential explanations include inadequate treatment frequency, misclassification of disease activity, lesion characteristics, pharmacological tolerance, and activation of alternative angiogenic pathways. True anti-VEGF tachyphylaxis appears less common than the broader concept of incomplete therapeutic response.

Switching agents can improve anatomical outcomes in selected refractory eyes. A systematic review and meta-analysis of eyes with treatment-resistant nAMD switched from bevacizumab or ranibizumab to aflibercept demonstrated significant reductions in central retinal thickness, although improvements in visual acuity were relatively modest [37]. This distinction is clinically important: improved OCT anatomy does not necessarily translate into substantial functional recovery once irreversible retinal damage has occurred.

Treatment switching should therefore be individualized and based on persistent disease activity, treatment interval requirements, previous therapeutic response, and anatomical characteristics rather than fluid alone.

Long-Term Safety

Repeated intravitreal anti-VEGF therapy has an overall favorable safety profile. Serious ocular adverse events—including infectious endophthalmitis, retinal detachment, lens injury, and severe intraocular inflammation—are uncommon when injections are performed using appropriate aseptic technique.

Systemic VEGF suppression has raised theoretical concerns regarding arterial thromboembolic events, including myocardial infarction and stroke, particularly in elderly patients with underlying cardiovascular disease. However, systematic reviews and meta-analyses have generally not demonstrated a convincing major increase in cardiovascular events associated with intravitreal anti-VEGF therapy at commonly used ophthalmic doses [38,39]. Individualized assessment remains appropriate in patients with recent stroke, myocardial infarction, or substantial vascular risk.

Thus, for most patients with active nAMD, the risk of irreversible visual loss from withholding effective therapy substantially exceeds the known systemic risk of treatment.

Economic and Healthcare-System Burden

The chronic nature of nAMD places substantial economic pressure on healthcare systems. Costs include medication, OCT imaging, repeated clinical assessments, injection procedures, transportation, caregiver support, and indirect costs related to visual disability.

Differences in reimbursement, drug availability, clinic capacity, and national healthcare infrastructure contribute

to geographic variation in treatment intensity and outcomes. Real-world evidence continues to demonstrate that inadequate injection frequency and delayed follow-up are major contributors to the gap between trial efficacy and routine clinical effectiveness [40].

Cost-effective biosimilars, longer-duration anti-VEGF agents, streamlined Treat-and-Extend protocols, and home-monitoring technologies may therefore improve both treatment accessibility and long-term visual outcomes.

The principal challenges affecting long-term anti-VEGF treatment and potential strategies to address them are summarized in Table 4.

Table 4. Major Challenges Affecting Long-Term Anti-VEGF Therapy and Potential Strategies

Challenge	Effect on long-term outcomes	Potential strategy
High treatment burden	Treatment fatigue and reduced adherence	Treat-and-Extend; longer-duration agents
Undertreatment	Recurrent exudation and cumulative retinal injury	Proactive individualized therapy
Loss to follow-up	Irreversible visual deterioration	Education, reminders, caregiver support
Macular atrophy	Progressive irreversible central vision loss	OCT monitoring and preservation of disease control
Subretinal fibrosis	Permanent structural and functional damage	Early diagnosis and continuous suppression of CNV
Persistent disease activity	Recurrent fluid and retinal injury	Reassess diagnosis, interval and anti-VEGF agent
Incomplete treatment response	Anatomical persistence with limited functional gain	Selective switching and individualized management
Long-term safety concerns	Potential treatment hesitation or discontinuation	Individualized systemic risk assessment
Economic/health-system burden	Reduced treatment intensity and access	Biosimilars, durable agents and efficient care pathways

Overall, the major challenge in long-term nAMD management is no longer demonstrating that anti-VEGF therapy works, but ensuring that effective disease suppression can be maintained for many years without excessive treatment burden. Preventing undertreatment, maintaining follow-up, minimizing recurrent exudative injury, and addressing macular atrophy and fibrosis are therefore central to preserving long-term visual function [33–40].

5. EMERGING STRATEGIES AND FUTURE PERSPECTIVES

The remarkable success of anti-VEGF therapy has transformed neovascular age-related macular degeneration (nAMD) into a chronic, manageable disease. Nevertheless, the need for frequent intravitreal injections, progressive structural retinal damage, and declining long-term visual outcomes have driven the development of novel therapeutic strategies aimed at improving durability while reducing treatment burden. Recent advances focus on extending treatment intervals, targeting additional angiogenic pathways, improving drug delivery, and integrating emerging technologies into personalized patient care.

Faricimab: Dual-Pathway Inhibition

Faricimab represents the first bispecific antibody approved for nAMD that simultaneously inhibits vascular endothelial growth factor-A (VEGF-A) and angiopoietin-2 (Ang-2). While VEGF inhibition suppresses pathological neovascularization and vascular permeability, Ang-2 inhibition promotes vascular stabilization and may reduce inflammation and vascular leakage.

The phase III TENAYA and LUCERNE trials demonstrated that faricimab achieved visual acuity outcomes non-inferior to aflibercept while allowing treatment intervals of up to 16 weeks in a substantial proportion of patients [41,42]. Extension analyses and early real-world studies suggest that longer dosing intervals may reduce treatment burden without compromising anatomical or functional outcomes.

Although longer follow-up is still required, dual-pathway inhibition represents one of the most important advances in nAMD therapy over the past decade.

High-Dose Aflibercept (8 mg)

Increasing the intravitreal dose of aflibercept from 2 mg to 8 mg has emerged as another strategy for extending treatment durability. The PULSAR trial demonstrated that high-dose aflibercept maintained visual outcomes comparable to conventional dosing while enabling treatment intervals of up to 16 weeks in many patients [43].

The principal advantage of higher-dose therapy lies in prolonged VEGF suppression rather than superior visual gain. If long-term studies confirm sustained efficacy and safety, high-dose aflibercept may further reduce clinic visits and improve long-term treatment adherence.

Port Delivery System with Ranibizumab

The Port Delivery System (PDS) was developed to provide continuous intraocular release of ranibizumab

through a surgically implanted refillable reservoir. In the ARCHWAY trial, patients receiving the implant achieved visual outcomes comparable to monthly ranibizumab while requiring refilling only every 24 weeks [44].

Although the PDS substantially reduced injection frequency, concerns regarding device-related complications—including conjunctival erosion, endophthalmitis, and implant dislocation—have limited widespread clinical adoption. Ongoing refinement of implant design and surgical technique may improve the future role of sustained drug-delivery systems.

Gene Therapy

Gene therapy represents one of the most promising future approaches for reducing the lifelong treatment burden associated with anti-VEGF therapy. Rather than administering repeated intravitreal injections, viral vectors deliver genes encoding anti-angiogenic proteins directly to retinal cells, enabling sustained intraocular production after a single procedure.

Several investigational therapies—including RGX-314 and ADVM-022 (Ixo-vec)—have demonstrated encouraging early-phase results, with reduced injection requirements while maintaining acceptable visual outcomes [45,46]. However, longer follow-up remains necessary to establish durability, long-term safety, and optimal patient selection before routine clinical implementation.

Biosimilars

The increasing economic burden of anti-VEGF therapy has stimulated development of biosimilar agents. Ranibizumab biosimilars—including SB11 and FYB201—have demonstrated comparable efficacy, safety, pharmacokinetics, and immunogenicity to the reference product in randomized clinical trials [47].

Biosimilars may substantially improve global treatment accessibility, particularly in healthcare systems with limited financial resources. Wider availability of lower-cost therapies may also reduce undertreatment, one of the principal causes of inferior long-term visual outcomes.

Precision Medicine

Precision medicine is increasingly being incorporated into retinal imaging and clinical decision-making. Deep learning algorithms can accurately identify retinal fluid, classify disease activity, quantify structural biomarkers on OCT, and predict the need for retreatment with high accuracy [48]. Precision medicine approaches integrating imaging biomarkers, genetics, systemic risk factors, and treatment history may ultimately allow clinicians to tailor therapy to each patient's biological characteristics rather than applying uniform treatment schedules.

Home OCT and Teleophthalmology

Remote disease monitoring has gained increasing attention as healthcare systems seek to reduce clinic burden while maintaining early detection of recurrent disease activity. Home OCT devices, smartphone-based vision monitoring, and teleophthalmology platforms may allow earlier recognition of recurrent exudation, reducing unnecessary clinic visits while preventing delayed retreatment [49].

Although currently limited to selected patient populations, advances in remote retinal imaging and cloud-based image analysis may significantly alter future management strategies, particularly for elderly patients with limited mobility.

Future Research Priorities

Despite substantial progress, several important questions remain unanswered. Ultimately, the future of nAMD management is likely to involve durable pharmacological therapies combined with individualized treatment guided by advanced retinal imaging and predictive analytics.

The principal emerging therapies are summarized in Table 5.

Table 5. Emerging Therapeutic Strategies for Improving Long-Term Outcomes in nAMD

Therapy	Mechanism	Potential advantage	Current status
Faricimab	Dual VEGF-A/Ang-2 inhibition	Longer treatment intervals	Approved
Aflibercept 8 mg	Higher-dose VEGF inhibition	Extended durability	Approved in multiple regions
Port Delivery System	Continuous ranibizumab release	Reduced injection frequency	Limited clinical use
Gene therapy	Sustained intraocular anti-VEGF production	Potential one-time treatment	Phase II/III clinical trials
Ranibizumab biosimilars	Equivalent VEGF inhibition	Reduced treatment cost	Approved
Artificial intelligence	Imaging analysis and treatment prediction	Personalized management	Rapid clinical development
Home OCT	Remote retinal monitoring	Earlier recurrence detection	Emerging technology

Collectively, these advances indicate that the future management of nAMD will extend beyond repeated anti-VEGF injections toward individualized, durable, and technology-assisted treatment strategies. By reducing treatment burden while maintaining disease control, these innovations have the potential to further improve long-term visual outcomes and quality of life for patients with chronic neovascular AMD.

6. CONCLUSION

Neovascular age-related macular degeneration has evolved from an inevitably blinding disease into a chronic condition in which long-term visual preservation is achievable through sustained anti-VEGF therapy. Landmark randomized clinical trials established the efficacy of VEGF inhibition during the first two years of treatment, while subsequent extension studies and large real-world registries have provided valuable insight into the challenges of maintaining these gains over five to ten years and beyond.

Current evidence indicates that long-term visual outcomes depend not only on the pharmacological effectiveness of anti-VEGF agents but also on timely diagnosis, baseline visual acuity, treatment intensity, adherence, structural retinal preservation, and prevention of recurrent neovascular activity. Progressive macular atrophy, subretinal fibrosis, undertreatment, and loss to follow-up remain the principal causes of late visual decline despite continued therapy.

The widespread implementation of proactive Treat-and-Extend strategies has improved the balance between efficacy and treatment burden, while newer therapies—including dual-pathway inhibition, high-dose aflibercept, sustained drug-delivery systems, gene therapy, biosimilars, and artificial intelligence-assisted management—offer promising opportunities to further improve long-term outcomes.

Ultimately, successful long-term management of nAMD requires an individualized, patient-centered approach that combines evidence-based pharmacological therapy with careful retinal imaging, proactive retreatment, sustained patient engagement, and continuous adaptation to disease progression. As therapeutic innovation continues, future strategies should focus not only on controlling neovascular activity but also on preserving retinal structure and visual function throughout the patient's lifetime.

REFERENCES

1. Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng CY, Wong TY. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(2):e106-e116. doi:10.1016/S2214-109X(13)70145-1.
2. Ferris FL III, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, Sadda SR. Clinical classification of age-related macular degeneration. Ophthalmology. 2013;120(4):844-851. doi:10.1016/j.ophtha.2012.10.036.
3. Flaxel CJ, Adelman RA, Bailey ST, Fawzi A, Lim JI, Vemulakonda GA, Ying GS. Age-related macular degeneration Preferred Practice Pattern®. Ophthalmology. 2020;127(1):P1-P65. doi:10.1016/j.ophtha.2019.09.024.
4. Campochiaro PA, Soloway P, Ryan SJ, Miller JW. The pathogenesis of choroidal neovascularization in patients with age-related macular degeneration. Mol Vis. 1999;5:34.
5. Miller JW. Age-related macular degeneration revisited—piecing the puzzle: the LXIX Edward Jackson Memorial Lecture. Am J Ophthalmol. 2013;155(1):1-35.e13.
6. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med. 2004;351(27):2805-2816. doi:10.1056/NEJMoa042760.
7. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1419-1431. doi:10.1056/NEJMoa054481.
8. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1432-1444. doi:10.1056/NEJMoa062655.
9. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364(20):1897-1908. doi:10.1056/NEJMoa1102673.
10. Comparison of Age-related Macular Degeneration Treatments Trials Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119(7):1388-1398. doi:10.1016/j.ophtha.2012.03.053.
11. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, Reeves BC; IVAN Study Investigators. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet. 2013;382(9900):1258-1267.
12. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006.
13. Busbee BG, Ho AC, Brown DM, Heier JS, Suñer IJ, Li Z, Rubio RG, Lai P; HARBOR Study Group. Twelve-month efficacy and safety of 0.5-mg or 2.0-mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology. 2013;120(5):1046-1056.
14. Dugel PU, Koh A, Ogura Y, Jaffe GJ, Schmidt-Erfurth U, Brown DM, et al; HAWK and HARRIER Study Investigators. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology. 2020;127(1):72-84. doi:10.1016/j.ophtha.2019.04.017.
15. Dugel PU, Singh RP, Koh A, Ogura Y, Weissgerber G, Gedif K, et al. HAWK and HARRIER: ninety-

six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology. 2021;128(1):89-99. doi:10.1016/j.ophtha.2020.06.028.
16. Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K; SEVEN-UP Study Group. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). Ophthalmology. 2013;120(11):2292-2299. doi:10.1016/j.ophtha.2013.03.046.
17. Comparison of Age-related Macular Degeneration Treatments Trials Research Group, Maguire MG, Martin DF, Ying GS, Jaffe GJ, Daniel E, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the CATT study. Ophthalmology. 2016;123(8):1751-1761.
18. Chandra S, Arpa C, Menon D, Khalid H, Hamilton R, Nicholson L, et al. Ten-year outcomes of antivascular endothelial growth factor therapy in neovascular age-related macular degeneration. Eye (Lond). 2020;34(10):1888-1896. doi:10.1038/s41433-020-0764-9.
19. Finger RP, Puth MT, Schmid M, Barthelmes D, Guymer RH, Gillies MC. Lifetime outcomes of anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration. JAMA Ophthalmol. 2020;138(12):1234-1240. doi:10.1001/jamaophthalmol.2020.3989.
20. Nichani PAH, Popovic MM, Dhoot AS, Pathak A, Muni RH, Kertes PJ. Treat-and-extend dosing of intravitreal anti-VEGF agents in neovascular age-related macular degeneration: a meta-analysis. Eye (Lond). 2023;37(14):2855-2863. doi:10.1038/s41433-023-02439-6.
21. Wykoff CC, Croft DE, Brown DM, Wang R, Payne JF, Clark L, Abdelfattah NS, Sadda SR; TREX-AMD Study Group. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. Ophthalmology. 2015;122(12):2514-2522. doi:10.1016/j.ophtha.2015.08.009.
22. Heier JS, Khanani AM, Quezada Ruiz C, Basu K, Ferrone PJ, Brittain C, et al; TENAYA and LUCERNE Investigators. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration: TENAYA and LUCERNE. Lancet. 2022;399(10326):729-740. doi:10.1016/S0140-6736(22)00010-1.
23. Lanzetta P, Korobelnik JF, Heier JS, Leal S, Holz FG, Clark WL, et al. Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration (PULSAR): 48-week results from a randomised, double-masked, non-inferiority, phase 3 trial. Lancet. 2024. doi:10.1016/S0140-6736(23)02837-6.
24. Ying GS, Huang J, Maguire MG, Jaffe GJ, Grunwald JE, Toth C, et al; CATT Research Group. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology. 2013;120(1):122-129.
25. Chew EY, Clemons TE, Bressler SB, Elman MJ, Danis RP, Domalpally A, et al; AREDS2-HOME Study Research Group. Randomized trial of a home monitoring system for early detection of choroidal neovascularization: the HOME study. Ophthalmology. 2014;121(2):535-544. doi:10.1016/j.ophtha.2013.10.027.
26. Chandra S, Rasheed R, Menon D, Patrao N, Lamin A, Gurudas S, et al. Impact of injection frequency on 5-year real-world visual acuity outcomes of aflibercept therapy for neovascular age-related macular degeneration. Eye (Lond). 2021;35(2):409-417.
27. Wykoff CC, Ou WC, Brown DM, Croft DE, Wang R, Payne JF, et al. Randomized trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: 2-year results of the TREX-AMD study. Ophthalmol Retina. 2017;1(4):314-321.
28. Hatz K, Prünte C. Treat and extend versus pro re nata regimens of ranibizumab and aflibercept in neovascular age-related macular degeneration: a comparative study. Graefes Arch Clin Exp Ophthalmol. 2017;255(4):697-704.
29. Jaffe GJ, Martin DF, Toth CA, Daniel E, Maguire MG, Ying GS, et al; CATT Research Group. Macular morphology and visual acuity in the second year of the Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology. 2013;120(9):1860-1870.
30. Grunwald JE, Pistilli M, Daniel E, Ying GS, Pan W, Jaffe GJ, et al; CATT Research Group. Incidence and growth of geographic atrophy during 5 years of Comparison of Age-related Macular Degeneration Treatments Trials. Ophthalmology. 2017;124(1):97-104.
31. Ramakrishnan MS, Yu Y, VanderBeek BL. Association of visit adherence and visual acuity in patients with neovascular age-related macular degeneration. JAMA Ophthalmol. 2020;138(3):237-242.
32. Spooner K, Hong T, Wijeyakumar W, Chang AA. Switching to aflibercept among patients with treatment-resistant neovascular age-related macular degeneration: a systematic review with meta-analysis. Clin Ophthalmol. 2017;11:161-177. doi:10.2147/OPTH.S125676.
33. Spooner K, Broadhead G, Fraser-Bell S, Hong T, Wong JG, Chang AA. Real-world 10-year outcomes of anti-VEGF therapy for neovascular age-related macular degeneration: a meta-analysis. Clin Exp Ophthalmol. 2025;53(7):773-790. doi:10.1111/ceo.14559.
34. Holekamp NM, Liu Y, Yeh WS, Chia Y, Kiss S, Almony A, Kowalski JW. Clinical utilization of anti-VEGF agents and disease monitoring in neovascular age-related macular degeneration. Am J Ophthalmol. 2014;157(4):825-833.e1.
35. Obeid A, Gao X, Ali FS, Aderman CM, Shahlaee A, Adam MK, et al. Loss to follow-up among patients with neovascular age-related macular degeneration

who received intravitreal anti-VEGF injections. JAMA Ophthalmol. 2018;136(11):1251-1259.
36. Grunwald JE, Daniel E, Huang J, Ying GS, Maguire MG, Toth CA, et al; CATT Research Group. Risk of geographic atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials. Ophthalmology. 2014;121(1):150-161.
37. Spooner K, Hong T, Wijeyakumar W, Chang AA. Switching to aflibercept among patients with treatment-resistant neovascular age-related macular degeneration: systematic review and meta-analysis. Clin Ophthalmol. 2017;11:161-177. doi:10.2147/OPTH.S125676.
38. Thulliez M, Angoulvant D, Le Lez ML, Jonville-Béra AP, Pisella PJ, Gueyffier F, Béjan-Angoulvant T. Cardiovascular events and bleeding risk associated with intravitreal antivascular endothelial growth factor monoclonal antibodies: systematic review and meta-analysis. JAMA Ophthalmol. 2014;132(11):1317-1326.
39. Dalvin LA, Starr MR, AbouChehade JE, Damento GM, Garcia M, Shah SM, et al. Association of intravitreal anti-vascular endothelial growth factor therapy with risk of stroke, myocardial infarction, and death in patients with exudative age-related macular degeneration. JAMA Ophthalmol. 2019;137(5):483-490. doi:10.1001/jamaophthalmol.2018.6891.
40. Gohil R, Crosby-Nwaobi R, Forbes A, Burton B, Hykin P, Sivaprasad S. Treatment satisfaction of patients undergoing ranibizumab therapy for neovascular age-related macular degeneration in a real-life setting. Eye (Lond). 2016;30(5):715-719.
41. Heier JS, Khanani AM, Quezada Ruiz C, Basu K, Ferrone PJ, Brittain C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration: TENAYA and LUCERNE. Lancet. 2022;399(10326):729-740. doi:10.1016/S0140-6736(22)00010-1.
42. Khanani AM, Kotecha A, Chang A, Chen SJ, Chen Y, Guymer R, et al; TENAYA and LUCERNE Investigators. TENAYA and LUCERNE: two-year results from the phase 3 neovascular age-related macular degeneration trials of faricimab with treat-and-extend dosing in year 2. Ophthalmology. 2024;131(8):914-926. doi:10.1016/j.ophtha.2024.02.014.
43. Lanzetta P, Korobelnik JF, Heier JS, Leal S, Holz FG, Clark WL, et al. Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration (PULSAR): 48-week results from a randomised, double-masked, non-inferiority, phase 3 trial. Lancet. 2024. doi:10.1016/S0140-6736(23)02837-6.
44. Regillo C, Berger B, Brooks L, Clark WL, Mittra R, Wykoff CC, et al. Archway phase 3 trial of the Port Delivery System with ranibizumab for neovascular age-related macular degeneration: 2-year results. Ophthalmology. 2023;130(7):735-747. doi:10.1016/j.ophtha.2023.02.024.
45. Campochiaro PA, Avery R, Brown DM, Heier JS, Ho AC, Huddleston SM, et al. Gene therapy for neovascular age-related macular degeneration by subretinal delivery of RGX-314: a phase 1/2a dose-escalation study. Lancet. 2024;403(10436):1563-1573. doi:10.1016/S0140-6736(24)00310-6.
46. Finocchio L, Zeppieri M, Gabai A, Toneatto G, Spadea L, Salati C. Recent developments in gene therapy for neovascular age-related macular degeneration: a review. Biomedicines. 2023;11(12):3221. doi:10.3390/biomedicines11123221.
47. Woo SJ, Veith M, Hamouz J, Ernest J, Zalewski D, Studnička J, et al. Efficacy and safety of a proposed ranibizumab biosimilar product versus reference ranibizumab for patients with neovascular age-related macular degeneration: a randomized clinical trial. JAMA Ophthalmol. 2021;139(1):68-76.
48. Schmidt-Erfurth U, Bogunović H, Sadeghipour A, Schlegl T, Langs G, Gerendas BS, et al. Machine learning to analyze the prognostic value of current imaging biomarkers in neovascular age-related macular degeneration. Ophthalmol Retina. 2018;2(1):24-30.
49. Heier JS, Holekamp NM, Busquets MA, Elman MJ, Schechet SA, Ladd BS, et al. Pivotal trial validating usability and visualization performance of home OCT in neovascular age-related macular degeneration: report 1. Ophthalmol Sci. 2025;5(5):100772. doi:10.1016/j.xops.2025.100772.