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REVIEW ARTICLE

Update on the Use of Anti-Angiogenic Agents in Retinal Diseases: From Standard Therapy to New Strategies

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ABSTRACT

Introduction: anti-angiogenic agents have revolutionized the treatment of exudative retinal diseases over the past two decades.
Objective: to describe the most recent scientific evidence on the use of anti-angiogenic agents in retinal diseases.
Methods: a systematic review of the literature from 2020–2025 on anti-angiogenic agents in retinal diseases was conducted, identifying 156 articles from different databases, of which 28 were selected for their timeliness, relevance, and quality.
Development: recent literature confirms that anti-angiogenic therapies have transformed the management of retinal diseases by improving and maintaining visual acuity. However, they still face significant limitations such as the high burden of injections, heterogeneity in clinical response, and the occurrence of geographic atrophy with prolonged use. In response, innovative approaches are being developed, including combinations of molecules with complementary mechanisms, exploration of targets beyond vascular endothelial growth factor, and the incorporation of gene therapies aimed at sustained release, with the goal of optimizing visual outcomes and reducing treatment frequency.
Conclusions: the future of anti-angiogenic management is moving toward treatment personalization, reduction in administration frequency, and addressing broader pathophysiological mechanisms.

Keywords: Macular Degeneration; Macular Edema; Angiogenesis Inhibitors.

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INTRODUCTION

Exudative retinal diseases, characterized by an abnormal increase in vascular permeability and pathological neovascularization, are major causes of irreversible visual loss globally.[1] Neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusions (RVOs) represent the most prevalent clinical entities, being the main indications for intravitreal therapy.[2]

The socioeconomic burden of these conditions is considerable due to the deterioration in the quality of life of patients, who experience impairment in essential activities such as reading, driving, and facial recognition. Visual dependence for daily activities increases the risk of depression, social isolation, and accidents, multiplying the impact on public health systems.[3]

The discovery of vascular endothelial growth factor (VEGF) as a key mediator in angiogenesis and vascular permeability radically transformed the treatment of these diseases.[4] Previously, therapeutic options such as laser photocoagulation or photodynamic therapy showed limited efficacy. Understanding the role of VEGF in the formation of abnormal choroidal neovessels and macular edema allowed the development of targeted therapies, transforming the visual prognosis for millions of patients.[5]

The introduction of anti-VEGF agents, starting with pegaptanib and later with more potent molecules such as ranibizumab, bevacizumab and aflibercept, paradigmatically changed clinical practice, allowing not only the stabilization but also the improvement of visual acuity.[6] This advance represents one of the most successful examples of translational medicine in the 21st century, where research in vascular biology materialized into treatments that substantially modified clinical outcomes.[7]

However, accumulated experience has revealed significant challenges in the long-term management of anti-VEGF therapy. The chronic nature of these conditions requires repeated intravitreal injections, frequently monthly or through treat-and-extend regimens, imposing a substantial burden on patients, caregivers, and healthcare systems.[8,9] This burden often results in suboptimal treatment adherence and less frequent monitoring, leading to less favorable visual outcomes than those observed in controlled clinical trials.[10]

Additionally, approximately 10-15 % of patients with AMD treated with anti-VEGF do not respond adequately to standard therapy, experiencing persistence or recurrence of subretinal or intraretinal fluid despite regular treatment.[11] This refractoriness represents a complex clinical problem that demands therapeutic alternatives. Furthermore, prolonged use of anti-VEGF has been associated with progressive geographic atrophy of the retinal pigment epithelium, limiting long-term visual benefits.[12,13]

These challenges have motivated intense research into new therapeutic strategies, including longer-acting molecules that allow extended dosing intervals, agents that act on alternative pathways of angiogenesis and vascular permeability, sustained-release systems that minimize the frequency of injections, and personalized medicine approaches to optimize treatment according to individual patient characteristics.[14,15] The present research aims to describe the most recent scientific evidence on the use of antiangiogenic agents in retinal diseases, analyzing the available molecules, current dosing regimens, emerging strategies and pending challenges, providing a comprehensive perspective of the current state and future directions of this dynamic field of ophthalmology.

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METHODS

A systematic review of the scientific literature on antiangiogenic agents in retinal diseases was carried out during the period 2020-2025. The search was performed in the PubMed, Scopus and SciELO databases, using the following descriptors according to MeSH and DeCS terms: "anti-VEGF agents", "antiangiogenic agents", "age-related macular degeneration", "diabetic macular edema", "retinal vein occlusion", "intravitreal therapy", "ranibizumab", "aflibercept", "brolucizumab", "faricimab".

Inclusion criteria included randomized controlled trials, prospective observational studies, systematic reviews, and meta-analyses published in English or Spanish; research evaluating the efficacy, safety, or dosing regimens of anti-VEGF drugs; and studies with a minimum follow-up of six months. Case reports, letters to the editor without original data, and studies with a high probability of methodological bias were excluded.

The initial screening identified 156 potentially relevant articles using the search strategy. After removing duplicates and reviewing titles and abstracts, 62 articles were shortlisted for detailed evaluation. Finally, 28 studies were included that met the inclusion criteria and demonstrated the highest methodological quality and clinical relevance.

Data extraction was performed using a standardized form that recorded: study characteristics (design, population, sample size), interventions evaluated, main outcomes (visual acuity, central retinal thickness), adverse events, and main conclusions. The methodological quality of clinical trials was assessed using the Jadad scale, while observational studies were evaluated using the Newcastle-Ottawa scale.

The synthesis of evidence was organized by disease type (AMD, DME, OVR) and by thematic categories: established anti-VEGF molecules, new anti-angiogenic agents, dosing regimens, strategies in suboptimal responders, and emerging long-release therapies.

DEVELOPMENT

The establishment of ranibizumab, bevacizumab, and aflibercept as therapeutic cornerstones is not only a historical fact but also a dynamic clinical reality, continually reinforced by real-world and long-term effectiveness data. The pivotal ANCHOR, MARINA, and VIEW studies marked this shift, while clinical practice evidence and extension trials such as CATT and IVAN confirmed their efficacy and long-term sustainability. These results show that, even with less frequent injections compared to the initial monthly protocol, most patients maintain visual gains, thanks to retinal "anatomical memory" that ensures functional stability with less intensive regimens.[7]

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The choice of agent in daily clinical practice is a sophisticated exercise in evidence-based medicine, logistics, and health economics. The CATT study, a pioneering study that directly compared ranibizumab and bevacizumab, established practical equivalence in visual efficacy for age-related macular degeneration (AMD), although ranibizumab had a slightly more favorable safety profile in some parameters, specifically a lower rate of serious systemic adverse events, even though the absolute difference was small.[8] This functional equivalence, coupled with its significantly lower cost (often a fraction of the price of its competitors), has solidified bevacizumab as the mainstay of treatment in resource-constrained healthcare systems and a valid and ethical option in many others. Its use has democratized access to highly effective therapy.

For its part, aflibercept, with its ingenious decoy receptor design that confers a higher binding affinity for VEGF-A (approximately 100 times greater than that of ranibizumab or bevacizumab) and the ability to also block VEGF-B and Placental Growth Factor (PlGF), represented an evolutionary step. The VIEW studies demonstrated its non-inferiority to monthly ranibizumab with a dosing regimen every two months (following a loading phase of three monthly injections).[9,16,17] This pharmacodynamic characteristic not only supported a less frequent treatment regimen but also prompted its preferential use in cases where persistent macular edema, considerable central retinal thickness (CRT), or a suboptimal response to first-line agents is observed. It is postulated that, in these scenarios, more potent and prolonged suppression of VEGF, along with the blockade of additional PlGF-mediated inflammatory pathways, may be clinically decisive. Retrospective real-world studies have supported this notion, showing that a significant percentage of patients "non-responders" to ranibizumab or bevacizumab achieve anatomical and functional improvement when switching to aflibercept.[18]

The quest for longer treatment intervals is the holy grail in managing these chronic diseases, with the dual goal of preserving the patient's vision and quality of life by reducing the treatment burden. The last few years have seen the arrival of two innovative agents that represent two distinct development philosophies.

Brolucizumab represented a significant technological advance as the first single-chain viral antibody (scFv) approved for ophthalmology. Its small molecular size (26 kDa, compared to 48 kDa for ranibizumab or 115 kDa for aflibercept) allows for the administration of a higher molar concentration of drug in the standard intravitreal injection volume (6.0 mg/0.05 mL). Theoretically, this promotes greater tissue penetration into the retina and an extended duration of action due to more efficient binding and slower clearance. The phase 3 HAWK and HARRIER studies conclusively met their primary endpoint, demonstrating the non-inferiority of brolucizumab administered every 12 weeks compared to aflibercept every 8 weeks in patients with age-related macular degeneration (AMD). Anatomically, brolucizumab showed superiority in reducing GCR from week 16 to 48, and most importantly, it managed to maintain the 12-week interval in more than 50 % of patients in the first year.[10]

Initial enthusiasm for brolucizumab waned after the detection of serious and unusual intraocular inflammatory events in clinical practice, such as occlusive retinal vasculitis and vascular occlusion, with a risk of irreversible vision loss. The actual incidence (2–4 %) was higher than in clinical trials, peaking at two to three months post-injection. This safety profile compelled clinicians to carefully assess the risk-benefit ratio, educate patients about warning signs, and implement close monitoring via peripheral ophthalmoscopy. Consequently, the drug is primarily used as a second-line treatment or in selected cases. This experience underscores that efficacy and duration of action, along with post-marketing pharmacovigilance, must be considered as essential requirements for clinical safety.[11]

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Faricimab marks a genuine paradigm shift as the first and only bispecific agent designed for ophthalmology. Its innovation lies not only in its longer duration of action but also in a mechanism of action that simultaneously addresses two central pathogenic pathways: the VEGF-A pathway (angiogenesis and vascular permeability) and the Angiopoietin-2 (Ang-2) pathway. Ang-2 acts as a contextual antagonist of the Tie2 tyrosine kinase receptor. Under physiological conditions, Ang-1 activates Tie2, promoting vascular stability and maturity. However, in pathological stress environments such as hypoxia (present in age-related macular degeneration, AMD) or hyperglycemia (in diabetic macular edema, DME), Ang-2 levels increase dramatically, competing with Ang-1 and destabilizing blood vessels. This destabilization synergizes with the effects of VEGF, exacerbating vascular leakage, inflammation, and neovascularization.[12]

Dual inhibition of VEGF-A and Ang-2 aims not only to "dry out" the retina but also to actively promote greater vascular stability, addressing a pathophysiological pillar that has not yet been treated pharmacologically. The phase 3 clinical trials TENAYA and LUCERNE for AMD and YOSEMITE and RHINE for DME have been conclusive. They demonstrated that faricimab, with a personalized dosing regimen that can be extended to every 16 weeks (based on anatomical criteria of disease activity), achieved non-inferior visual outcomes to aflibercept administered every eight weeks. Furthermore, superior anatomical improvements were observed, with a higher proportion of patients achieving a normal GCR and a greater mean reduction in thickness.[13,14]

Faricimab has demonstrated in diabetic macular edema studies that most patients can achieve prolonged treatment intervals (75 % ≥12 weeks and more than 50 % ≥16 weeks), positioning itself as an innovative option that comprehensively addresses vascular instability and has a safety profile comparable to aflibercept, without the signs of inflammation observed with brolucizumab. Accumulated experience has driven the transition from fixed monthly regimens or PRN schemes, limited by fluid recurrences and logistical burden, towards more dynamic and personalized strategies. In this context, the Treat-and-Extend protocol has become globally established as the dominant strategy, anticipating recurrence and allowing progressively longer intervals while maintaining a dry and stable retina.[15]

This approach individualizes therapy according to the disease behavior in each patient, recognizing that there is significant heterogeneity in the rate of recurrence. Studies such as TREX-AMD confirmed that T&E is as effective as the monthly regimen in terms of long-term visual gain, but with a significantly lower median number of annual injections (approximately 9-10 vs. 13), improving treatment efficiency without compromising outcomes.[16] Subsequent real-world evidence, such as the extensive study by Gillies et al. that included thousands of patients, has consolidated this strategy, showing its applicability and efficacy with different anti-VEGF agents in routine clinical practice, achieving lasting visual stability with a sustainable treatment burden.[17]

When a patient exhibits an incomplete response (persistent macular edema despite frequent injections) or becomes a "high-demand phenomenon" (requiring very short treatment intervals, less than six to eight weeks, to remain dry), it is imperative to reassess the therapeutic strategy. This scenario, often erroneously termed "resistance," suggests a more complex pathophysiology where pathways beyond VEGF are playing a significant role. Switching agents is a common and evidence-based practice. Transitioning from ranibizumab or bevacizumab to aflibercept may benefit a subgroup of patients, possibly due to its greater VEGF-A binding potency or the inhibition of additional factors such as PlGF, which is implicated in inflammation and resistance to anti-VEGF agents.[18]

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With the advent of faricimab, this option has been greatly enhanced, offering a fundamentally different mechanism of action. Switching to faricimab can be particularly useful in cases where a strong inflammatory component or vascular instability is suspected, such as in patients with large pigmented neovessels or with a persistent poor anatomical response to conventional anti-VEGF agents. Combination therapies represent another logical approach with a solid pathophysiological basis. Combining an anti-VEGF agent with intravitreal corticosteroids, such as the dexamethasone implant (Ozurdex®) or triamcinolone, is based on targeting multiple pathways simultaneously. While anti-VEGF targets VEGF-mediated vascular permeability specifically, corticosteroids act on inflammation more broadly and potently, inhibiting the expression of multiple pro-inflammatory cytokines (such as IL-6, TNF-alpha), chemokines, and other vascular permeability factors (such as the angiopoietin family), in addition to restoring blood-retinal barrier function through the induction of tight junction proteins (such as occludin). In patients with refractory DME, this combination has been shown in studies such as that by Boyer et al. to allow for faster and more sustained anatomical improvement and significantly reduce the frequency of anti-VEGF injections required.[19]

The choice of this strategy must be carefully weighed against the risk profile of steroidal side effects, which include elevated intraocular pressure (which may require hypotensive treatment) and accelerated cataract formation, especially in phakic patients. Another emerging strategy for suboptimal response is supplemental laser photocoagulation of the neovascular membrane. Techniques such as subthreshold thermal laser or selective photocoagulation of feeder vessels identified by indocyanine green angiography can, in selected cases, reduce exudative activity and allow for longer intervals between injections. However, this approach requires considerable technical expertise and is not without risk of damage to adjacent photoreceptors.

The Ranibizumab Port Delivery System (PDS) was a conceptual milestone that changed the mindset regarding what was possible in the treatment of chronic retinal diseases. This intravitreal implant, about the size of a grain of rice, functioned as a reservoir that released ranibizumab continuously and in a controlled manner into the vitreous cavity. The pioneering phase 2 Ladder trial demonstrated that this system could maintain refill intervals of 6 months or more, freeing the patient from the physical and psychological burden of repeated injections.[20]

The Phase 3 ARCHWAY trials confirmed that the PDS with six-month refills was non-inferior to monthly ranibizumab injections. However, design challenges (complicated refill events requiring a surgical procedure) and a safety profile that included a higher rate of device-related endophthalmitis and proliferative vitreoretinopathy led the company to withdraw it from the market. Despite this, its legacy is profound and indelible: it validated the clinical feasibility, patient acceptance, and medical demand for sustained-release therapies, decisively driving research and development in other platforms such as biodegradable microparticles, slow-release hydrogels, and novel long-lasting implants.

Gene therapy aims to be the definitive solution to the burden of chronic treatment, with the goal of single or very infrequent administration. The predominant strategy involves using viral vectors, mainly adeno-associated viruses (AAVs) of retinal-trophic serotypes (such as AAV2 and AAV8), to deliver a therapeutic gene encoding an anti-angiogenic protein directly to retinal cells (mainly retinal pigment epithelium cells or ganglion cells). The aim is to transform these cells into "biological factories" that continuously and locally produce the drug, maintaining stable therapeutic concentrations in the eye for years, ideally for life.[21]

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Several candidates are in advanced stages of clinical research.

- ADVM-022 (from Adverum Biotechnologies) uses an AAV.27m8 vector to express a version of the aflibercept protein. Clinical trial data (OPTIC for AMDen) have shown a manageable safety profile, with intraocular inflammation being the most common adverse event, generally controllable with corticosteroids. Most significantly, it has demonstrated a dramatic reduction in the need for conventional anti-VEGF booster injections, with the vast majority of patients free of rescue therapy for at least the first 1.5 years of follow-up.[22]
- RGX-314 (from Regenxbio): Uses the AAV8 vector to express a ranibizumab-like monoclonal antibody fragment. It is administered subretinal (in early trials) and, more promisingly and less invasively, suprachoroidally. Results have been equally encouraging, showing a sustained reduction in annualized anti-VEGF growth rates, with a safety profile that is being refined to manage inflammatory responses.[23]

The future challenges for gene therapy are formidable. It will be crucial to ensure the long-term safety of viral transfection and continuous gene expression (risk of chronic inflammation or retinal atrophy), to precisely control the level and duration of expression (avoiding both underdosing and chronic overexpression), and, no less challenging, to make this cutting-edge technology affordable and covered by healthcare systems. The future of treatment lies not only in longer duration but also in greater precision.

The research focuses on identifying and blocking new gene therapy targets involved in pathological angiogenesis and inflammation. These include:

- Connective tissue growth factor (CTGF/CCN2): a key mediator in fibrosis and scarring, processes that lead to irreversible visual impairment in late stages of age-related macular degeneration (AMD). The CTGF inhibitor, pegpleranib (RXI-109), is being investigated in combination with anti-VEGF to prevent scar formation.
- Complement Pathway: Strong genetic evidence links uncontrolled activation of the complement system (especially the alternative pathway) with dry and neovascular AMD. Drugs such as pegcetacoplan (APL-2) and avacincaptad pegol (Zimura) are being evaluated to reduce geographic atrophy in the dry form and potentially modulate neovascular activity in the wet form.
- Integrins: cell adhesion molecules that play a role in the survival and migration of endothelial cells. Risutoplanib (LHA-510) is an investigational integrin inhibitor.

In parallel, advances in multimodal imaging techniques (spectral-domain optical coherence tomography - OCT, OCT angiography, autofluorescence) are enabling the identification of predictive biomarkers of treatment response. Characteristics such as the type of neovascularization (type 1, 2, or 3), the presence of double layers in the ellipsoid line, or specific fluid patterns can predict which patients will be "high-demanders" or respond better to a dual inhibitor such as faricimab compared to a traditional anti-VEGF.[23] This "precision medicine" will allow, in the future, the assignment of the most appropriate treatment to each patient from the outset, optimizing outcomes and resources.

The evolution of treatment for exudative retinal diseases reflects both the success of translational research and the complexity of addressing chronic, multifactorial pathologies: anti-VEGF agents revolutionized prognosis, but suboptimal responses highlighted the need for broader approaches. In this context, faricimab marks a conceptual shift by combining VEGF inhibition with Ang-2 modulation, offering longer intervals between treatments and greater vascular stability, while the experience with brolucizumab underscored the priority of safety over convenience. Gene therapy promises to radically transform the landscape, although it faces technical, regulatory, and equity challenges. Therefore, the most viable immediate path is to optimize current tools

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through treatment and evaluation protocols supported by AI, predictive biomarkers, and rational combination therapies. This moves us toward a personalized and proactive model whose objective is not only to dry the retina but also to achieve sustained remissions with minimal therapeutic burden, preserving vision and quality of life.

CONCLUSIONS

Anti-angiogenic therapy for retinal diseases is evolving rapidly, with agents such as ranibizumab, bevacizumab, and aflibercept becoming established due to their proven efficacy and safety. Newer molecules like brolucizumab and faricimab aim to reduce the frequency of administration, although they require ongoing safety monitoring. The current trend is toward personalized therapies, with the Treat-and-Extend regimen standing out as the optimal strategy, along with the use of agent changes or combinations in suboptimal responders. The future includes sustained-release therapies and gene therapy, with great transformative potential. Research is essential to overcome resistance, identify biomarkers, and ensure equitable access to these advances.

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