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Advances in Anti-VEGF Therapy for the Treatment of Neovascular Age-Related Macular Degeneration

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ABSTRACT

The current standard of care for neovascular age-related macular degeneration (nAMD) heavily depends on anti-VEGF agents. Maintaining early visual gains, however, is a clinical struggle. Recurrent fluid, subretinal fibrosis, and macular atrophy add to a slow decline in sight although ongoing intravitreal injections. This review investigates how modern medicine attempts to lower this treatment burden by adopting next-generation molecules, updated monitoring routines, and sustained-release hardware. Following PRISMA guidelines, I reviewed 14 main English articles from the last 15 years. In the eye, too much VEGF-A damages the blood-retina barrier, causing fluid to leak into the retina. Standard treatments are good at clearing this fluid, but over time, the drugs often become less effective. To counter this, modern drug development focuses on prolonging dose intervals. Although brolucizumab is highly effective at reducing fluid, it carries a risk of intraocular inflammation. Faricimab targets two pathways (Ang-2 and VEGF-A), which strengthens blood vessels and lets certain patients extend their treatment intervals to 16 weeks. Furthermore, OCT imaging confirms that trace amounts of fluid are safe to tolerate. In the future, continuous treatments like permanent surgical ports and gene therapy could completely change long-term care for people with nAMD.

Keywords: "neovascular age-related macular degeneration" (nAMD), "wet AMD", "anti-VEGF therapy", "ranibizumab", "aflibercept", "brolucizumab", "faricimab", "optical coherence tomography" (OCT), and "disease activity criteria".

1. INTRODUCTION

Anti-VEGF therapy is the main treatment for people with neovascular age-related macular degeneration (nAMD). However, long-term data show that treating this condition over many years is difficult, defined by ups and downs. Even when patients receive repeated eye injections, their average vision usually does not stay at the good level it was when they started treatment. Instead, patients experience a gradual decline in visual acuity over time. This happens mainly because the leaking fluid often comes back, subretinal scars (fibrosis) begin to form, and the macula starts to waste away (atrophy) (Spooner et al., 2025; Tsiropoulos et al., 2026).

To maintain vision stability, patients must receive their shots regularly and follow the treatment plan exactly. Keeping up with the clinic schedule heavily influences how well a person will see in the long run. Even though the treatment

becomes less effective as time passes, continuing anti-VEGF therapy for up to 10 years remains highly useful because it prevents patients from losing their sight completely (Spooner et al., 2025).

At the same time, examining long-term data causes several major problems. In many medical studies, a large number of patients drop out of the study and stop attending the clinic during follow-up. This incomplete data makes it much harder to do deep meta-analyses. Also, treatments and drugs have improved over the years, which makes it difficult to apply old study findings to today's patients. Another problem is that past studies did not use a single, standardized rule to measure and document macular atrophy. Most study groups also lack diversity, meaning there is very little information about patients of Asian or African descent. Finally, although anti-VEGF injections are widely used, scientists have not fully studied how they affect the inner layers of the retina, including the nerve fibers and ganglion cells (Tsiropoulos et al., 2026). Recent studies also point out the necessity to find novel approaches to prevent vascular leakage and angiogenesis (Yamada, 2022). This paper will examine recent progress in anti-VEGF care to better understand these long-term issues.

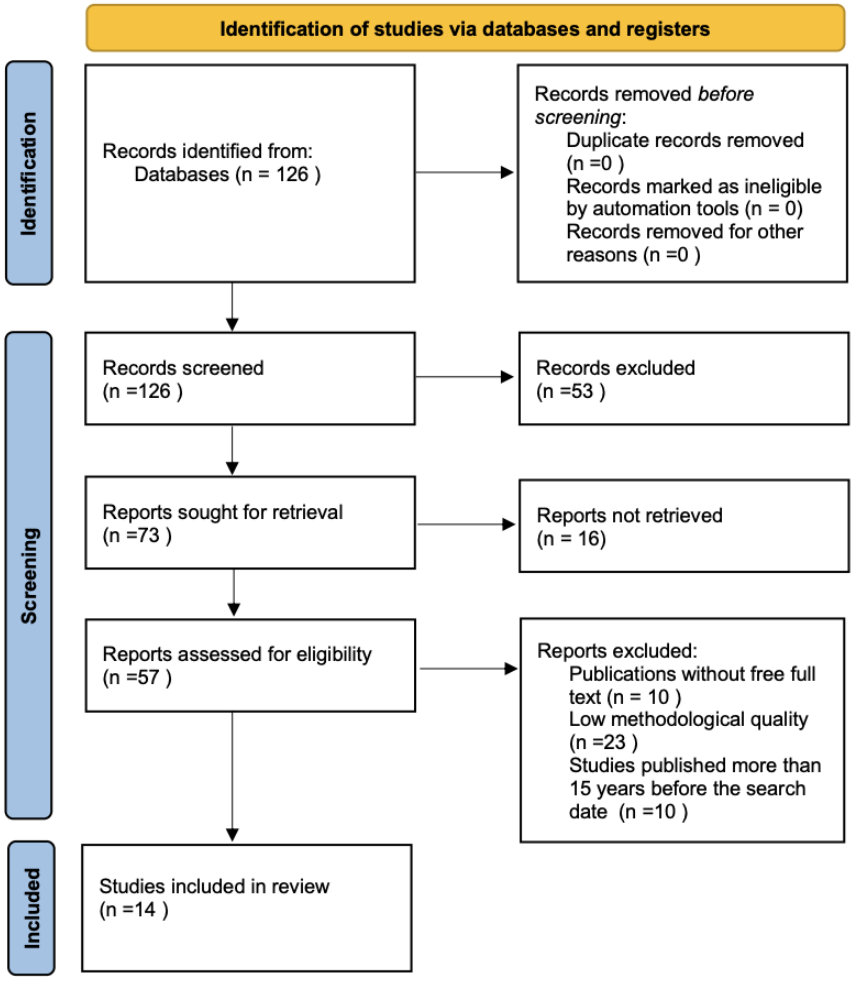

Figure 1. PRISMA flowchart

2. REVIEW METHODS

Search Strategy

My search strategy utilized specific keywords to find relevant literature: "neovascular age-related macular degeneration" (nAMD), "wet AMD", "anti-VEGF therapy", "ranibizumab", "aflibercept", "brolucizumab", "faricimab", "optical coherence tomography" (OCT), and "disease activity criteria". I searched databases to cover the biological and anatomical basis of exudative retinal diseases. If focused specifically on how different anti-VEGF medicines and long-acting drug delivery devices affect eye tissues, retinal fluids, and patient vision.

Inclusion and Exclusion Criteria

I included English-language full-text publications from the last 15 years (2011–present). This period experienced the development of new multi-target therapies, high-dose drugs, and permanent ocular implants, which changed how doctors handle wet AMD. This review prioritized systematic reviews, meta-analyses, narrative reviews, and randomized controlled trials (RCTs)—including major phase 3 trials such as VIEW, HAWK & HARRIER, TENAYA & LUCERNE.

Study Selection and Data Extraction

All the information presented in this paper comes from peer-reviewed scientific studies that met these criteria. My initial database search identified 126 records. Then, 53 articles were selected for full-text evaluation. Based on the inclusion and exclusion rules, 14 publications were included in the final text synthesis. Figure 1 shows the entire selection process in a standard PRISMA flow diagram.

3. RESULTS AND DISCUSSION

Mechanisms of Action of Anti-VEGF Drugs in Eye Tissues

The Role of VEGF Isoforms (Mainly VEGF-A) and Its Effect on the Blood-Retina Barrier

The human retina has a very high oxygen demand and a high metabolic rate. To maintain its microenvironment, the retina is separated from the general circulation by a protective barrier called the blood-retina barrier (BRB). The BRB is divided into two main components: the inner blood-retina barrier (iBRB), which consists of endothelial cells lining the inner retinal blood vessels, and the outer blood-retina barrier (oBRB), which is formed by retinal pigment epithelium (RPE) cells.

In a healthy eye, RPE cells naturally secrete vascular endothelial growth factor (VEGF) to maintain the physical integrity and stability of the nearby choriocapillaris blood vessels. However, in diseases such as wet age-related macular degeneration (nAMD), a high level of VEGF-primarily, VEGF-A-drives the pathological growth of abnormal new blood vessels beneath the retina. This abnormal process of vessel growth is known as choroidal neovascularization (CNV) (O'Leary & Campbell, 2023; Yang et al., 2016). Table 1 provides a summary of the primary anti-VEGF drugs and prospective long-acting therapies evaluated in this study, presenting their mechanisms and key characteristics.

Table 1. Summary of Modern Anti-VEGF Therapeutics and Delivery Systems

Therapy / Device	Mechanism of Action	Primary Target(s)	Key Clinical Characteristics
Ranibizumab	Monoclonal antibody fragment	VEGFA (all isoforms)	Standard first-line therapy; requires frequent dosing.
Aflibercept	Recombinant fusion protein	VEGFA, VEGFB, PGF	High binding affinity; established Treat-and-Extend (T&E) regimens.
Brolucizumab	Single-chain antibody fragment	VEGFA	Strong drying effect; significant risks of intraocular inflammation.
Faricimab	Bispecific monoclonal antibody	VEGFA, Ang-2	Dual pathway inhibition stabilizes vessels; allows up to 16-week intervals.
Port Delivery System (PDS)	Surgically implanted permanent port	VEGFA (ranibizumab)	Continuous release up to 6 months; carries surgical complication risks.
Gene Therapy (AAV)	Viral vector gene delivery	Self-producing anti-VEGF	Potential one-time treatment; currently in clinical trials (e.g., RGX-314).

The Impact of Therapy on Retinal Anatomy: Reducing Intraretinal and Subretinal Edema

When VEGF levels get too high, the tiny seals between blood vessels start to break. As a result, fluid and blood proteins leak directly into the retina. The fluid just pools up inside the retina (IRF) or right underneath it (SRF). All this extra fluid makes the eye swell up. It also makes the center part of the eye thicker than it should be. This distorts the natural shape of the retina and impairs vision (O'Leary & Campbell, 2023; Yang et al., 2016; Kim et al., 2023).

To monitor these changes, doctors use specialized scans called SD-OCT. These pictures let them measure exactly how much fluid is trapped and check the thickness of the eye. In fact, checking the amount of fluid is the main way doctors tell how active the disease actually is (Kim et al., 2023).

On the other hand, some anatomical changes, such as the volume of a pigment epithelial detachment (PED), are much more rigid and might show no significant changes even after multiple months of regular anti-VEGF treatment (Kim et al., 2023).

Mechanisms of Resistance (Tachyphylaxis): Why Response to Classic Drugs Decreases

Even though anti-VEGF injections are the first-line treatment for managing nAMD, many patients experience a slow loss of drug effectiveness after receiving repeated injections over time. Persistent fluid or recurrent leakage remains common in spite of ongoing standard therapy. This reduction in treatment response is usually caused by two distinct clinical and pharmacological phenomena: tachyphylaxis and drug tolerance (Kim et al., 2023; Yang et al., 2016).

Tachyphylaxis is an acute, sudden decrease in the therapeutic response to a drug immediately after its administration. It can happen very early in the treatment cycle, sometimes after just two injections. Simply increasing the drug dose cannot overcome tachyphylaxis. Instead, doctors can restore the drug's efficacy by pausing treatment for a short period, adjusting the dose intervals, or switching the patient to a different anti-VEGF drug. Switching between drugs such as ranibizumab, bevacizumab, or aflibercept can restore anatomical response because these agents differ in molecular size, binding properties, and distribution within retinal tissue (Yang et al., 2016).

On the other hand, drug tolerance is a slower process where the body's response to a stable concentration of a drug decreases after long-term, repeated use. Tolerance is divided into pharmacokinetic and pharmacodynamic types. Pharmacokinetic tolerance happens when less of the active drug physically reaches its target site. This can occur because the eye clears the drug too quickly or because the patient develops an immune response that generates neutralizing antibodies against the anti-VEGF agent (Yang et al., 2016).

Pharmacodynamic tolerance occurs when the biological pathways inside the eye adapt to the drug. For example, macrophages within the abnormal tissue can respond to VEGF inhibition by upregulating their own VEGF production, or the tissue can express more VEGF receptors. Furthermore, the eye can shift its growth cues to alternative, redundant proangiogenic factors-such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor (TGF), or interleukins- which trigger vessel growth completely independent of VEGF (Yang et al., 2016).

Evolution of Anti-VEGF Molecules and Disease Pathogenesis

Classic Drugs as a Baseline: Ranibizumab and Bevacizumab (Off-Label)

Wet age-related macular degeneration (wAMD) is a major cause of vision loss and legal blindness worldwide. The first anti-VEGF drug approved for this condition was pegaptanib in 2004, which targeted only one isoform, VEGFA165. However, pegaptanib became obsolete after pan-VEGF blockers were introduced, as these newer drugs could bind all VEGFA isoforms as well as provided much better vision outcomes for patients.

Among these classic pan-VEGF drugs, ranibizumab and bevacizumab became the standard treatments. Bevacizumab was originally created to treat colon cancer, but doctors have used it off-label for neovascular AMD since 2005. Because one single vial of bevacizumab can be split into smaller doses for the eye, it is a much cheaper option than other treatments. Studies have shown that bevacizumab is effective and noninferior to ranibizumab, so it is often chosen as a first-line agent. However, for some patients, bevacizumab might not dry the retina as effectively or last as long as other available agents. Ranibizumab was developed specifically for the treatment of eye conditions. It is a humanized monoclonal antibody fragment which targets all VEGFA isoforms. Clinical trials such as MARINA and ANCHOR showed that ranibizumab improves vision (Kaiser et al., 2021).

Even so, real-world studies show that it is hard to replicate those excellent vision gains over the long term in everyday clinical practice. This happens because patients face a heavy treatment burden from frequent eye checks and injections, which often leads to undertreatment (Kaiser et al., 2021; Baumal et al., 2023; Khanani et al., 2024).

Breakthrough with Aflibercept (2 mg): The Standard of Treat-and-Extend (T&E) Regimens

To address the need for less frequent dosing, aflibercept (2 mg) was approved in 2011. This drug is a recombinant fusion protein composed of parts of the human VEGFR1 and VEGFR2 receptors combined with an IgG1 Fc domain. It is designed to act like a trap, binding to VEGFA, VEGFB, and placental growth factor (PGF). Because of this unique structure, aflibercept has a very high binding

affinity for its targets (Kaiser et al., 2021). Aflibercept was the first anti-VEGF drug to be officially evaluated with an extended injection schedule, like every 8 weeks, after the initial loading doses. Clinical studies proved that it is noninferior to monthly ranibizumab injections. This success helped establish flexible dosing schedules in daily practice, especially the Treat-and-Extend (T&E) regimen. In a T&E schedule, doctors can gradually adjust the time between injections based on the patient's actual disease activity, consequently reducing the number of clinic visits while continuing retinal stability (Kaiser et al., 2021; Khanani et al., 2024).

Newer Drugs: Brolucizumab, Faricimab, and Waiting Longer Between Shots

The main goal with the newest eye treatments is pretty simple: make them last longer in the eye. That way, patients don't have to come in for injections nearly as often. Drug developers pull this off using a handful of tricks. They might tweak the size of the molecules, or engineer the medicine so it binds its target much more tightly. Another approach is to develop a single drug that blocks multiple disease triggers simultaneously (Kaiser et al., 2021; Khanani et al., 2024).

Brolucizumab (6 mg) was approved in 2019 as a single-chain antibody fragment targeting VEGFA. Because its molecular weight is very low (26 kDa), scientists can achieve a much higher molar concentration within a tiny 0.05 mL injection volume. In fact, it delivers a much higher dose than larger molecules such as bevacizumab or ranibizumab. Clinical trials HAWK and HARRIER showed that brolucizumab is noninferior to aflibercept and can maintain a 12-week treatment interval in more than half of patients. Real-world data also confirm that brolucizumab has a very strong drying effect, significantly lowering central subfield thickness (CST) and removing intraretinal fluid (IRF) and subretinal fluid (SRF) in both treatment-naive eyes as well as eyes that have switched from other drugs. But there is a huge catch when it comes to safety. When doctors actually started using brolucizumab in regular clinics, they noticed some bad side effects. The drug can severely inflame the inside of the eye. It can also cause blood vessels to swell up or even get completely blocked. Because of these serious issues, some patients permanently lose their vision (Kaiser et al., 2021; Baumal et al., 2023).

Faricimab is a massive step forward for eye care. At a 6.0 mg dose, it is actually the very first eye injection designed to do two jobs at once. Older drugs just block one target, called VEGF. Faricimab, on the other hand, shuts down both VEGF-A and another troublemaker named Ang-2. When a person's eye gets sick, that Ang-2 protein really messes things up. It leaves the blood vessels swollen, weak, and constantly leaking. Because Faricimab stops both of these bad proteins at the exact same time, it toughens up the blood vessels way better than the standard drugs we used to rely on. To make sure this double-action approach actually worked, scientists ran two huge two-year studies, called TENAYA and LUCERNE. The results were clear. If doctors customize the schedule for each person, faricimab keeps their eyesight sharp while needing way fewer shots than aflibercept. In fact, by the end of the two years, more than half of the patients (about 59% to 67%) could safely wait a full 16 weeks between their visits. Interestingly, clinical data show that just making the anti-VEGF dose higher does not automatically make it last longer; for example, a 4-fold higher anti-VEGF dose in the HARBOR and CANDELA trials failed to improve treatment durability, which suggests that faricimab's long-lasting effect is truly caused by its dual pathway inhibition (Khanani et al., 2024).

Other emerging options look at different ways to extend therapy intervals. Conbercept is a fusion protein approved in China that adds a special receptor domain to bind tightly to VEGFA, VEGFB, and PGF, though its global trials failed to show a benefit at 12-week intervals compared to aflibercept every 8 weeks. Abicipar pegol is a recombinant DARPin with a long half-life in the eye of about 13 days, but it was not approved by the FDA due to a high rate of intraocular inflammation. KSI-301 is an anti-VEGF antibody-biopolymer conjugate with an extremely large molecular weight of 950 kDa, which gives it high intraocular stability and allows more than half of wAMD patients in early trials to go 6 months without needing another treatment. Finally, instead of regular injections, scientists developed the ranibizumab port-delivery system (PDS, Susvimo), a permanent device surgically implanted into the eye wall. It slowly releases a high concentration of ranibizumab over time, and the phase 3 ARCHWAY trial showed that 98% of patients could go 6 months before needing a refill, though there are still safety concerns about vitreous hemorrhage related to the surgical technique (Kaiser et al., 2021).

Therapy Efficacy Markers and Patient Monitoring

Imaging Biomarkers (SD-OCT / OCT-A): Subretinal Fluid, Intraretinal Fluid, and Central Retinal Thickness as Indicators of Disease Activity

Optical coherence tomography (OCT) is the most common tool doctors use to check and monitor patients with neovascular age-related macular degeneration (nAMD). OCT helps detect specific structural changes in the eye, called biomarkers, that indicate the disease's activity. When nAMD is active and leaking, fluid builds up in different parts of the retina: inside the retinal layers as intraretinal fluid,

under the retina as subretinal fluid, or under the retinal pigment epithelium (RPE) layer as a pigment epithelial detachment (PED) (Metrangolo et al., 2021).

Central retinal thickness (CRT) was among the first parameters doctors measured with OCT scans. When CRT changes rapidly up and down, it indicates the disease is active, and these frequent thickness changes may impair the patient's final vision. However, CRT is not always the best way to estimate final vision because it measures all layers of the eye together rather than focusing on specific fluid problems. Looking closely at where the fluid is actually located provides much better treatment guidance (Metrangolo et al., 2021).

Intraretinal cystoid fluid (IRC) looks like small pockets or cysts in the inner parts of the retina. IRC is a highly dangerous sign for a patient's sight. Having IRC at the very start of treatment usually means the patient already has poor vision and will not improve much even after anti-VEGF injections. If these fluid cysts persist in the eye beyond the first three months of treatment, vision can worsen, and the patient faces a high risk of developing permanent scars (fibrosis) or tissue loss (atrophy) (Metrangolo et al., 2021).

Subretinal fluid (SRF) differs because it collects beneath the retina, directly above the RPE layer. Patients with SRF often achieve better vision and less tissue loss than those with IRC. In fact, a major clinical study, FLUID, showed that doctors do not need to dry up every single drop of SRF. Patients with a small amount of subretinal fluid remaining in the center of the macula did just as well as those with completely dry retinas. Another study, the CATT study, found that patients with foveal SRF at baseline had better vision even after 5 years of follow-up. Researchers believe this fluid might act as a cushion, protecting the retinal photoreceptor cells from the sick RPE layer below, or it might contain proteins that nourish the retina. Lastly, fluid under the RPE that causes a PED does not seem to affect vision choices as much as IRC or SRF (Metrangolo et al., 2021). Given the complexity of evaluating these fluid compartments on OCT, recent advancements in artificial intelligence are increasingly being utilized to automate fluid quantification and accurately predict optimal treatment intervals (Urbańska et al., 2024).

Functional Endpoints: Best Corrected Visual Acuity (BCVA) Measured on ETDRS Charts

When researchers test these eye drugs, they mainly check a patient's vision using a specific letter chart called an ETDRS chart. In fact, doctors rely heavily on these letter scores to figure out a person's everyday treatment schedule (Patel et al., 2023).

Even though everyone uses BCVA, it has some clear weak points. First, measuring vision with letter charts can change a lot from one visit to the next just by chance, especially in older patients with macular diseases. Second, vision loss happens late. The physical changes and fluid accumulation show up on an OCT scan much earlier, long before the patient actually struggles to read the letters on the chart. There is also a "ceiling effect" in vision testing. This means that patients who start treatment with very poor vision usually show a much larger jump in gained letters than patients who started with relatively good sight (Patel et al., 2023).

Modern Drug Delivery Systems and Prospective Innovations

Long-Acting Release Systems: The Port Delivery System (PDS)

Anti-VEGF injections are the first-line standard treatment for wet age-related macular degeneration. However, patients only get good vision results if they receive frequent injections and regular eye checks. This high frequency of treatments creates a heavy burden for patients, families, and doctors. In the real world, patients often get fewer injections than they actually need, which leads to worse vision benefits compared to clinical trials. To solve this problem, doctors need a treatment system that releases medicine constantly and reduces how often patients need a needle in their eye (Ranade et al., 2022).

The Port Delivery System with ranibizumab (PDS) is a permanent and refillable implant that is placed surgically into the eye wall at the pars plana. The device has a transparent body that holds about 20 μL of a custom ranibizumab formula. The medicine is released slowly into the eye through a porous titanium element. The drug travels from a high concentration area inside the device to a lower concentration area in the eye following Fick's law of diffusion. Tests show that using a high concentration of 100 mg/mL allows the device to release measurable amounts of drug for more than six months (Ranade et al., 2022).

When the medicine runs out, doctors can refill the device in the clinic using a custom refill needle. This special needle has two tubes inside it. It can pull out the old remaining fluid and push in fresh medicine at the same time in one single movement. This system is very efficient because a single 100 μL refill replaces more than 95% of the old fluid inside the implant with fresh drug. It also prevents a sudden extra dose of medicine from leaking directly into the eye during the refill process (Ranade et al., 2022).

In a large clinical trial called Archway, refilling the PDS device every six months gave patients the same vision results as getting regular monthly injections. Also, 93.2% of the patients said they preferred the PDS implant over getting regular eye shots. However, the PDS is not good for every patient. It cannot be used in people who have eye allergies, thin conjunctiva, or problems with their sclera.

Because it requires surgery, it also carries serious risks. The device has an official warning because patients with the implant had three times more eye infections (endophthalmitis) than patients who received regular injections. Additionally, other common anti-VEGF drugs like bevacizumab and aflibercept cannot be used with this device because they clump together over time and lose their strength (Ranade et al., 2022).

Future Therapies and Gene Therapy

Gene therapy is another option to provide a long-lasting anti-VEGF treatment. The main goal of this approach is to make the eye cells produce their own anti-VEGF medicine continuously after a single treatment. This could fix the economic and social problems caused by lifelong eye injections. To deliver the treatment, scientists use small, modified viruses called recombinant adeno-associated viral vectors (AAV). AAV vectors are very helpful because they give long-lasting medicine levels, have low toxic effects, and do not trigger a massive immune reaction. The most common types used in eye studies are AAV2, AAV5, and AAV8. One problem with AAV vectors is that they have a small storage space of about 4.6 kilobases, so they cannot carry very large genes (Guimaraes et al., 2021).

Doctors can inject these viral vectors into the eye using three different paths. First, subretinal delivery puts the virus under the retina, which creates a temporary separation of the tissue layers. This path is useful because it puts the treatment very close to the cells that need it most, and clinical data show it is safe and triggers very little inflammation. Second, intravitreal delivery injects the virus into the vitreous body. This path is easier, but a layer called the inner limiting membrane acts as a wall that stops the virus from spreading well. It also causes more inflammation and makes the body create antibodies that can block future treatments in the other eye. Third, suprachoroidal delivery injects the virus into a space between the choroid and the sclera using a special microinjector or catheter, allowing the medicine to spread around the back of the eye (Guimaraes et al., 2021).

Several gene therapies have been tested in humans. An early trial using an AAV5 virus to carry a gene called PEDF was safe and aided stabilization of eye lesions in a dose-dependent way. Another project used a subretinal injection of a virus carrying sFLT-1 (called AVA-101) and successfully lowered the number of extra injections patients needed. A study named ADVM-022 tested an intravitreal virus that makes the eye produce aflibercept. Patients in this trial did not need any rescue injections for up to 44 weeks, and their inflammation was mild and easy to treat with eye drops. Finally, a therapy called RGX-314 uses an AAV8 vector under the retina to produce a medicine similar to ranibizumab. In its highest dose group, 73% of the patients did not need any standard eye shots for six months while their vision and retinal thickness improved (Guimaraes et al., 2021).

Patient age is an important factor in these treatments. Older patients with wet AMD might have a weaker immune system, which can protect them from strong inflammatory reactions to the virus. However, older people are also more vulnerable to the side effects of any general immunosuppressant drugs given during surgery (Guimaraes et al., 2021).

4. CONCLUSION

In conclusion, anti-VEGF therapy is highly successful at repairing the broken blood-retina barrier and clearing dangerous fluid pockets in patients with neovascular age-related macular degeneration. While classic treatment plans face clear challenges from a heavy injection burden and drug tolerance, modern tracking tools like artificial intelligence are helping doctors find the perfect injection timing for each individual. Moving forward, the clinical introduction of multi-pathway drugs, permanent refillable port devices, and targeted viral gene therapies will dramatically lower the number of required hospital visits. Ultimately, these continuous drug-release breakthroughs will help eliminate real-world undertreatment and protect patient eyesight much more effectively over time.

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Authors' Contributions

This manuscript has been read and approved by the author. The authors believe that this manuscript represents honest work done by him.

Informed consent

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Ethical approval

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Conflict of interest

The author declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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