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Review

CURRENT STATUS OF CLINICAL TRIAL EVIDENCE FOR GENE IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION : A Scoping Review

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ABSTRACT

Introduction: Blindness is on the rise globally, with age-related macular degeneration (AMD) as the fourth leading cause. Conventional therapeutic strategies for neovascular AMD (nAMD) utilizes anti-VEGF proteins, however compliance is a known issue. This study aims to review current development on gene therapy as a new therapeutic strategy for nAMD to mitigate challenges regarding therapeutic compliance.

Methods: A scoping review was conducted in May 24th 2025, with articles obtained from PubMed, Google Scholar, Scopus, and Cochrane. Studies were limited to systematic reviews and meta-analysis, randomized control studies, non-randomized controlled studies, and observational studies.

Results: Three gene therapy studies evaluating RGX-314, ixoberogene soroparvovec, and rAAV.sFLT-1 were identified. Outcomes assessed included visual acuity (VA), central retinal thickness (CRT), recombinant protein expression, and annualized anti-VEGF injection rates. All 3 studies demonstrated an improved or stabilized VA and CRT. Follow-up duration ranged from 2 to 3 years. Three participants in the rAAV.sFLT-1 study were diagnosed with malignancy during the study period, however no causal relationship with gene therapy was established.

Conclusion: The use of the three gene therapies in managing nAMD demonstrates signals of biological activity and a reduced annualized anti-VEGF injection rate. These therapies hold a promising future strategy to counter nAMD management challenges, particularly the burden of compliance to repeated intravitreal anti-VEGF injections. Ultimately, a comprehensive phase 3 clinical trials is still vital for refining the efficacy and long-term safety monitoring prior to the utilization of these paradigm-shifting approach to nAMD therapy.

Keywords: gene therapy, neovascular age related macular degeneration, wet age related macular degeneration, exudative age related macular degeneration, nAMD

Introduction

Age-related macular degeneration (AMD) is one of the leading causes of visual impairment in adults above 60 years old. Age-related macular degeneration progressively affects central vision, causing declining detail accuracy and colour detection. Although initially it may be asymptomatic, its advanced stages can lead to blindness. Initially, intracellular lipofuscin accumulation and macular Drusens are found, which are a lipid deposition underneath the retinal pigment epithelium (RPE). Advanced AMD may manifest as dry AMD or wet AMD. Wet AMD or neovascular AMD (nAMD) shows presence of neovascularization under the RPE which may extend to the subretinal space. nAMD can further manifest as subretinal haemorrhage and intraretinal fluid accumulation, which may cause reversible vision loss. If untreated however, may lead macular scarring and irreversible vision loss.[1–4]

Globally, AMD is in fourth place of the cause of blindness, following cataract, glaucoma, and refractive error. The prevalence of AMD is 8.69% in adults age 45-85 years old.[5] As life expectancies progressively extend throughout the decades, causing an increase of the aging population, AMD poses a serious threat to global vision health. Although nAMD only accounts for 10% of AMD, 90% of nAMD cases is linked to severe vision loss.[1,6] AMD involves a multifactorial interplay between genetic and environmental factors.

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It has been established that AMD is not a monogenic disease as several genetic loci are hypothesized to be involved including the complement pathway, lipid metabolism, and extracellular matrix remodelling. AMD is most associated with polymorphism at 2 locus which are Tyr402His/p.Y402H and ARMS2/HTRA1.[7]

Treatment for nAMD has progressively developed these few decades, particularly in the development of antibodies against vascular endothelial growth factor (VEGF) and its receptors. VEGF plays a major role in exudation of nAMD, in the cascade leading to angiogenesis, vascular permeability, and inflammation. Anti-VEGFs inhibits these cascades, and have been proven useful as an intravitreal medication. Many anti-VEGF medications have been proven safe and effective in cases of nAMD. Several popular anti-VEGFs include bevacizumab, ranibizumab, aflibercept, brolucizumab, and faricimab. Despite development of these breakthrough drugs, anti-VEGFs fall short on maintaining drug compliance as it requires long term repeated injections and monitoring to maintain effectiveness.[8] Thus, the need of a new drug for nAMD to effectively combat disease progression and maintain therapeutical compliance is needed.

Gene therapy has been developed since 1990 and has proven success in diseases such as Leber's congenital amaurosis in 2008. Initially, gene therapy was aimed at diseases that can be treated by targeting a single gene. However, application of gene therapy in nAMD required a different strategy, as it is not a monogenic disease entity. Utilization of robust therapeutical strategies, such as targeting VEGFs to prevent disease progression, were integrated with the concept of gene therapy. Thus, gene therapy aiming for endogenous production of VEGF proteins were developed, in the hopes of overcoming the need for constant recurrent intravitreal injections.[9] Although there are currently a number of studies researching gene therapy in nAMD, the available evidence is still scattered. This study aims to explore current development on different choices of gene therapy for endogenous anti VEGF production in nAMD.

Methods

A scoping review was conducted in accordance to the guideline by the Joanna Briggs Institute (JBI) based on the Arksey and O'Malley framework and the Levac framework.[10] The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) checklist was used for guidance in reporting our scoping review.[11] We identify the Population, Concept, and Context for this study. The population is neovascular AMD patients, concept is role of gene therapy, and context is novel management of neovascular AMD.

This scoping review aims to include all studies related to our research question from the last five years for our initial search. The initial search was conducted on May 24th 2025, studies were obtained through a systematic search from databases including PUBMED, Google Scholar, Scopus, and Cochrane. A secondary search through references list of obtained studies was also conducted. Keywords with or without MeSH terms that have been used include "Neovascular Age Related Macular Degeneration", "Wet Age Related Macular Degeneration", "Gene Therapy", "Retinal Gene Therapy", "Adeno Associated Viral Vectors".

Inclusion criteria of our study include studies which: (1) provide novel gene therapies in the management of nAMD, (2) describe the underlying mechanism of such novel therapy, (3) provide information of current development of said novel technique, (4) be published in English. Study designs included were limited to randomized control studies, observational studies, non-randomized controlled cohort, and observational studies. Literature reviews were not included in the initial advanced search, however relevant reviews from the secondary search through reference list were included for the discussion. Studies from the initial search were limited from the past five years. Exclusion criteria include articles describing irrelevant outcomes (outdated therapies or unrelated topics of discussion), non-English articles, no full text availability, congress presentation, letter to editor and commentary. Our systematic search and study recruitment timeline is summarized in Figure 1

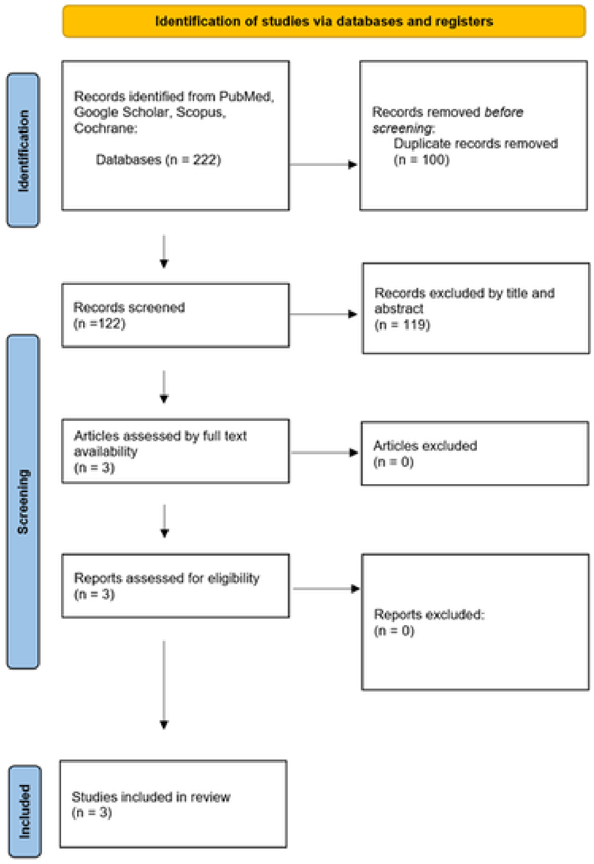

Figure 1 PRISMA flow chart of eligible studies for scoping review

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Result

Our initial search yielded 222 articles in total, afterwards duplicates were removed resulting in 122 articles. We then conducted manual screening of the titles and topics, excluding articles with irrelevant topics to our study. Many articles were excluded due to irrelevance of the article topic and study type. Lastly, we received a total of three articles with full text eligibility to be included in this scoping review. Table 1 summarizes general characteristics of the included studies.

The studies included in our review utilize gene therapy through different mechanisms. Campochiaro et al utilized RGX-314, which is a viral vector designed to contain a genetic sequence to produce anti-VEGF proteins closely comparable to ranibizumab. This adeno-associated virus serotype 8 vector thus can produce anti-VEGF-A antigens. Patients that have exhibited anatomic response to intravitreal ranibizumab were included to this study, to ensure likelihood to respond towards the produced ranibizumab-like protein. Meanwhile, Khanani et al utilized ixo-vec, formerly known as ADVM-022, which is a novel vector capsid AAV2.7m8 containing an ubiquitous expression cassette for aflibercept coding sequence. Patients initially were given intravitreal aflibercept as a 2 mg single dosage during screening, acting as part of standard care and evaluation of response towards aflibercept. Rakoczy et al utilizes rAAV.sFLT-1 which is a recombinant adeno-associated vector producing the protein sFLT-1. The produced sFLT-1 protein is a VEGFR1 receptor in a soluble form, with properties that can bind and inactivate VEGF-A, VEGF-B, and P1GF via domain 2, the same location utilized by aflibercept.[13] Key results on the targeted loci, produced proteins, and doses are summarized in Table 2.

Study Results

Gene therapy is a method of using genes to prevent or cure diseases, it is usually done by introducing new copies of the defected gene which will then integrate to the host cell. Gene therapy research for retinoid isomerohydrolase RPE65 gene for Leber's congenital amaurosis in 2008 has proven success and became the basis for further development of gene therapy.

Studies on gene therapy has further enriched our understanding of biologic viral vectors, one of which is the adeno-associated viral (AAV) vectors. AAV's consist of a single-stranded DNA genome containing a Rep and Cap gene positioned between two inverted terminal repeats (ITRs). AAV's require assistance of a helper virus for DNA replication. Rep and Cap are open reading frames which are transcribed and translated into virus life cycle proteins (including Rep 78, Rep68, Rep52, Rep40, VP1, VP2, and VP3).[7,15] Current strategies for ocular gene therapy include insertion of wild type copies of transgenes along with a promoter, in between two ITRs, with Rep and Cap added in trans.[7] Studies included within our review utilizes a series of different target recombinant genes and vectors. Different AAV2 and AAV8 strains were utilized and inserted with a specific transgene within the open reading frame.

Outcomes of safety and tolerability

All three studies mainly investigated the safety and tolerability of new gene therapy targets in nAMD. The study from Campochiaro exhibited no clinically observed ocular inflammation due to therapy. Treatment emergent adverse events (TEAEs) are listed within Table 3, which include retinal degeneration and retinal pigmentary changes. Retinal degeneration was found in 17% participants (n=7), including pigmentary changes (n=4), retinal pigment clumping (n=1), and decreased thickness at the bleb (n=2). Most were considered as possibly linked to RGX-314, due to surgical procedure, or related to both. Retinal pigmentary changes in the form of hypopigmentation or hyperpigmentation, was seen via ocular imaging in 69% (n=29) participants. Investigators considered it to be possibly linked to RGX-314 in 86% instances, possibly due to subretinal procedure in 21 participants.

Khanani revealed TEAEs were dose dependent, 87.3% were mild and 15.6% were moderate in severity. Most common were anterior chamber cells (16 participants) and vitreous cells (11 participants). Serious treatment emergent adverse events (SAEs) were found in 5 cases, including 2 cataracts, dry AMD, retinal detachment, and recurrent uveitis. Dry AMD and recurrent uveitis were deemed probably related to ixo-vec. None of the adverse events cause persistent visual decline. There were not any non-ocular TEAEs reported. At study completion 47% (7/15) participants in the high dose cohort were still given topical corticosteroids to treat ocular inflammation. Rakoczy reported three TEAEs including decreased immunoglobulins, eye irritation, and decrease in natural killer cell count. Thirty-three SAEs were reported, 15 were in the control group and 18 in gene therapy group. Within the gene therapy group, 2 patients had cancer at the point of enrolment who later died during or within the trial. Three patients from gene therapy group developed a cancer diagnosis within the trial, which were breast cancer, lung cancer, and colorectal cancer. None of the control group patients (n=13) reported cancer at enrolment and none were diagnosed within the study. However, the differences in proportion of cancer among groups were not statistically significant. Thus, the authors were unable to conclude the risk of cancer to the intervention.

Outcomes of visual acuity, central retinal thickness, protein concentrations, and injection rates

Our three studies also evaluated secondary outcomes in addition to the main purpose of evaluating safety and tolerability. Among the factors assessed within this study were visual acuity, CRT evaluated from OCT, retinal protein concentrations, and changes injection rates. Campochiaro and Khanani evaluated changes from baseline to 2 years post gene therapy injection. Mean changes of ETDRS level differences, CRT changes, protein concentration levels, and injection rates were not statistically analyzed (Table 4). Rakoczy presented secondary outcome data from three year follow up in the form of median data followed by a statistical analysis of the results. Visual acuity and CRT changes results were not statistically significant. Meanwhile for recombinant protein concentrations, Rakoczy reported a statistically significant decrease in saliva samples at the three years follow up, which was hypothesized due to technical difficulties in dilution.

Table 1 Characteristics of included studies

Author, year	Country	Study type	Treatment	Number of Patients	Starting therapy	Follow up period	Key Results
Campochiaro, 2024	USA	Multicenter phase 1/2a clinical trial, open label	Subretinal RGX-314, producing ranibizumab -like protein	42	Ranibi zumab	2 years	-Well tolerated -Improved BCVA and CRT -Sustained protein concentration in aqueous humour -Most common AEs were conjunctival haemorrhage and retinal pigmentary changes via ocular imaging.
Khanani, 2023	USA	Multicenter phase 1 clinical trial, open label, prospective	Intravitreal ixoberogene soroparvove c, producing aflibercept	30	Afliber cept	2 years	-Well tolerated -Stabilized BCVA and CRT -Anti-VEGF injections were reduced by 80% -AE was anterior chamber cells
Rakoczy, 2019	Australia	Single center, randomized control trial, phase 2a	Subretinal rAAV.sFLT-1	40	Ranibi zumab	3 years	-Well tolerated -Stabilized BCVA and CRT -3 patients from gene therapy group developed diagnosis of cancer during the trial

Table 2 Recombinant genes and utilized vectors in included studies

Author, year	Gene Therapy	Produced protein	Utilized vector	Dosage for each cohort	Method of delivery
Campochiaro, 2024	RGX-314	Ranibizumab-like protein	AAV8	1) 3×10^{9} genome copies/eye 2) 1×10^{10} genome copies/eye 3) 6×10^{10} genome copies/eye 4) 1.6×10^{11} genome copies/eye 5) 2.5×10^{11} genome copies/eye	Subretinal via vitrectomy
Khanani, 2023	ixoberogene soroparvovec (formerly ADVM-022)	Aflibercept	AAV2.7m8	1) 6×10^{11} vg/eye + prednisone 2) 2×10^{11} vg/eye + prednisone 3) 2×10^{11} vg/eye + topical difluprednate 4) 6×10^{11} vg/eye + topical difluprednate	Intravitreal
Rakoczy, 2019	rAAV.sFLT-1	sFLT-1, works on the same receptor domain as aflibercept	rAAV2	1) 1×10^{11} vg/eye 2) control	Subretinal via vitrectomy

Table 3. Safety profile of gene therapy studies

Author, year	Adverse events	Interpretation
Campochiaro, 2024	Clinical manifestation of immune response and drug related ocular inflammation were not found. TEAEs: • Conjunctival haemorrhage (69%), eye irritations (17%) and pain (17%) • Retinal degeneration (17%, n=7) was found in the form of ellipsoid manifestation in pigmented areas (n=4), retinal pigment epithelium clumping (n=1), and retinal decreased thickness at the bleb (n=2). • Retinal pigmentary changes such as hypopigmentation or hyperpigmentation via ocular imaging was seen in 69% (n=29) participant.	Subretinal RGX-314 was well tolerated.
Khanani, 2023	TEAEs: • Anterior chamber cells (16 participants) • vitreous cells (11 participants). SAEs: • 2 cataracts • dry AMD • retinal detachment • recurrent uveitis, dry AMD and recurrent uveitis were deemed probably related to ixo-vec. At study completion 47% (7/15) participants in the high dose cohort still required topical corticosteroids for treatment of inflammation.	Ixo-vec was well tolerated.
Rakoczy, 2019	TEAEs: decreased immunoglobulins, eye irritation, and decrease in natural killer cell count. SAEs: 15 were in the control group and 18 in gene therapy group. Cases of cancer identified within the gene therapy group: • 2 patients had cancer at the point of enrolment • 3 patients from gene therapy group developed cancer diagnosis within the trial None of the control group patients (n=13) reported cancer at enrolment and none were diagnosed within the study. Differences in proportion of cancer among groups were not statistically significant.	rAAV.sFLT-1 was well tolerated.

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Table 4. Secondary outcomes in included studies

Author, year	Cohorts for each study	Visual acuity	OCT results (CRT changes)	Recombinant protein concentration	Annualised injection rate	Supplemental injection rate
Campochiaro, 2024	**Cohort 1 (1):** 3 x 10^9 genome copies/eye **Cohort 2 (2):** 1 x 10^{10} genome copies/eye **Cohort 3 (3):** 6 x 10^{10} genome copies/eye **Cohort 4 (4):** 1.6 x 10^{11} genome copies/eye **Cohort 5 (5):** 2.5 x 10^{11} genome copies/eye	Mean difference in ETDRS letters among cohorts: (1) -8 (2) +1 (3) +14 (4) +1 (5) -4	Mean CRT differences among cohorts: (1) -89 um (2) +25 um (3) +2 um (4) -57 um (5) -108 um	Mean levels in aqueous 2 years post RGX-314 among cohorts: (1) 54.0 ng/mL (2) 88.8 ng/mL (3) 227.2 ng/mL (4) 272.8 ng/mL (5) 317.2 ng/mL	Mean differences among cohorts: (1) +10% (2) -3% (3) -62% (4) -59% (5) -79%	Mean need for supplemental ranibizumab injections among cohorts: (1) 10.3 injections per year (2) 9.3 injections per year (3) 2.8 injections per year (4) 4.4 injections per year (5) 2.0 injections per year
Khanani, 2023	**Low dose cohort:** 2 x 10^{11} vg/eye + oral/topical steroid. **High dose cohort:** 6 x 10^{11} vg/eye + oral/topical steroid.	Mean difference in ETDRS letters: Low dose: +0.2 (-4.6, 5.0) High dose: -0.2 (-3.4, 3.0)	Mean CRT differences: Low dose: -92.9 (-153.3, -32.6) High dose: -60.2 (-99.1, -21.3)	Aflibercept levels in aqueous humour remain stable at week 12. Data presented only represents a few individuals in the study.	Mean differences: Low dose: -80% (10.0 to 1.9) High dose: -98% (9.8 to 0.2)	Rate of participants who were free of supplemental injection: Low dose: 53% (8/15) High dose: 80% (12/15)
Rakoczy, 2019	**Cohort 1 (A):** given gene therapy with ≤2 anti-VEGF retreatment in their first year. **Cohort 2 (B):** given gene therapy with >2 anti-VEGF retreatment in their first year. **Control group (C):** not given gene therapy.	Median difference in ETDRS letters: (A) 63.5 to 54.0 (B) 53.5 to 36.0 (C) 61.5 to 41.0 No statistically significant difference between data points of any point of time.	Cohort 1 and control showed decrease in median CRT. Cohort 2 showed increase in median CRT. None of the results were statistically significant.	No statistically significant difference in concentration among gene therapy and control group in serum and urine sample. A statistically significant decrease in saliva samples.	N/A	Median number of needed retreatment injections: Cohort 1: 2.5 (1.0-2.0) Cohort 2: 11 (9.0-13.0) Control: 7.0 (6.0-11.0)

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Discussion

Utilization of gene therapy in nAMD targets production of different endogenous proteins with a series of antiviral vectors. Early phases of clinical trial that targets different genes and vectors is still being explored, such as sFLT-1 for by Rakoczy et al in 2015, which aims to create an endogenous production of the chimeric VEGF-neutralizing protein, halting the progression of nAMD. The produced sFLT-1 protein is a VEGFR1 receptor in a soluble form, with properties that can bind and inactivate VEGF-A, VEGF-B, and P1GF via domain 2, the same location utilized by aflibercept.[13,19–21] Recombinant adeno-associated vectors (rAAV) have been previously used in gene therapy studies for Leber's congenital amarousis and choroideraemia.[22] Thus, a version of rAAV was designed to encode for sFLT-1.[23–25] Studies on rAAV.sFLT-1 was continued by Rakoczy et al, observing subretinal gene therapy delivery up to a 3 year follow up period. Number of retreatment injections and losses of Early Treatment Diabetic Retinopathy Study (ETDRS) letters were compared among groups, in which the results did not suggest improvements among intervention group.[21]

In 2017, Heier et al studied AAV2-sFLT01 for intravitreal injection, utilizing the AAV2 vectors. AAV2 vectors are capable of transducing photoreceptors and retinal pigmented epithelium following subretinal administration, and transducing a subset of retinal ganglion cells and transitional epithelial cells of the pars plana following intravitreal administration. Heier et al's intravitreal delivery showed minimal change of BCVA at 1 year, with poor anatomic response to dosage given. This study also identified levels of AAV2 serum antibodies at baseline, which may potentially have a negative effect on the expression of transgenes such as low levels of transgene product and intraocular inflammation.[21,26] This study has demonstrated a higher dependency on dosage in intravitreal delivery, thus more studies have proceeded utilizing subretinal delivery for gene therapy.[26–29]

As treatment methods utilizing intravitreal anti-VEGF injections are proven effective, current strategies for gene therapy aim to modify the usage of the well-established proteins. In 2023, Khanani et al studied the development of ixoberogene soroparvovec (ixo-vec), which is a single dose gene therapy designed to encode continuous aflibercept production. Ixo-vec utilized a novel vector capsid, AAV2.8m8, which was engineered from AAV2 with properties to surpass the inner limiting membrane and have robust transduction of retinal cells (including photoreceptors, ganglion cells, bipolar cells, Muller cells, iris pigment epithelium, ciliary epithelium, and optic nerve cells). Ixo-vec is the first intravitreal gene therapy proven to have stable and durable expression of the anti-VEGF protein, aflibercept.[28,30,31] Within the OPTIC study, expression of intravitreal aflibercept remained stable at week 12 and a significantly decreased annualized injection rate was seen in the ixo-vec group.

Campochiaro et al developed the use of RGX-314, which is an AAV8 vector expressing for an anti VEGF-A antigen binding fragment similar to ranibizumab. This study utilized subretinal injection delivery and has shown promising RGX-314 protein concentration in the aqueous humour. Doses of 6 x 1010 genome copies per eye resulted in sustained anti-VEGF A concentrations, control of exudation, and visual acuity preservation. Meanwhile, doses under 2.5 x 1011 genome copies per eye have shown minimal ocular inflammation.[2]

Studies on gene therapy in nAMD are currently growing in numbers. Among the ongoing studies, several can be found listed on ClinicalTrial.gov with pending results. EXG102-031 utilizes rAAV expressing ABD-VEGFR fusion protein, targeted to neutralize all subtypes of VEGF, this study is currently in the phase 1/2a trial.[39] FT-003 utilizes an AAV vector and gene expression which is still undisclosed.[35] KH631utilizes rAAV8 expressing a VEGF receptor fusion protein binding affinity to VEGF-A, VEGF-B, and P1GF.[36.37] OLX10212 utilizes intravitreal delivery of cp-asiRNA, which targets the inflammatory pathways upstream of VEGF.[38] Currently, these studies are yet to publish results. However, the number of studies itself prove the global interest to pursue gene therapy as a potential breakthrough therapy for nAMD.

Conclusion

Gene therapy in nAMD trials are still in its infancy, with several prominent recombinant genes being RGX-314, ixoberogene soroparvovec, and rAAV.sFLT-1, generally showing favourable short-to mid-term safety profiles. These therapies demonstrate notable signals of biological activity including sustained intraocular anti-VEGF levels, stabilized VA and CRT, and lowered annual anti-VEGF injection rate. Adverse events are affected by the difference in transgenes and viral vectors. Gene therapy in nAMD may possibly address current challenges, notably the compliance towards repeated intravitreal anti-VEGF injections. Robust phase 3 clinical trials remain essential in testing clinical efficacy and long-term safety monitoring prior to implementation of these therapies for nAMD management.

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