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Disease Progression Pathways of Wet AMD: Opportunities for New Target Discovery

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Abstract

Introduction: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among people age 60 years or older in developed countries. Currently, anti-vascular endothelial growth factor (VEGF) therapy that inhibits angiogenesis and vascular permeability is the only treatment proven to increase visual acuity and arrest disease progression. Therapeutic limitations of anti-VEGF therapy include high costs, repeated intravitreal injections, and therapeutic ceilings and worsening vision outcomes despite aggressive treatment. As a result, there is a significant need to investigate other targets to address these limitations. Current molecules under investigation include targeting VEGF-C and VEGF-D, integrins, tyrosine kinase inhibitors, and the Tie2/Angiopoetin-2 pathway. A literature search was conducted through November 30, 2021 on PubMed, Medline, Google Scholar, and associated digital platforms with the following keywords: wet macular degeneration, age-related macular degeneration, therapy, VEGF-A, VEGF-C, VEGF-D, integrins, Tie2/Ang2, and tyrosine kinase inhibitors.

Areas covered: The authors provide a comprehensive review of AMD disease pathways and mechanisms involved in wet AMD as well as novel targets for future therapies.

Expert opinion: With novel targets and advancements in drug delivery, investigational efforts aiming to address the significant limitations of standard VEGF therapy-focused AMD disease management show great promise.

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Keywords

age-related macular degeneration; integrins; therapy; treatment; VEGF; tyrosine kinase inhibitors

1. Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible legal blindness among people older than 60 years in developed countries. The disease is projected to affect approximately 196 million people worldwide in 2020 and 288 million people by 2040.[1] AMD is typically categorized into two types—non-neovascular (non-exudative or dry) AMD and neovascular (exudative or wet) AMD (nAMD). nAMD is less prevalent than non-neovascular AMD, however, it causes more acute and severe loss of central vision. In nAMD choroidal neovascularization (CNV) develops under the macula, leading to an exudation of blood and fluid into the macula, scarring, and eventual central blindness.[2] This pathological vascular growth is driven by the upregulation of vascular endothelial growth factors (VEGF), which are cytokines that play a key role in angiogenesis and vascular permeability. The VEGF protein family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E, and placental growth factor, which act through the activation of tyrosine-kinase receptors. VEGF-A, in particular, plays a key role in regulating angiogenesis and vascular permeability in the eye as it promotes endothelial cell migration, proliferation, and survival.[2] As a result, VEGF-A is the current target of treatment for nAMD, and standard of care currently involves anti-VEGF-A monotherapy, specifically aflibercept, bevacizumab, and ranibizumab (Figure 1).

These current VEGF therapies, however, possess several significant limitations. First, anti-VEGF-A agents require frequent injections, causing a high treatment burden for patients and incomplete response due to an inability to keep up with the injection schedule.[3] Second, the injections cause significant patient anxiety and discomfort.[4] Furthermore, there are potential ocular risks associated with repeat injections, including sustained ocular hypertension, endophthalmitis, and retinal pigment epithelium (RPE) atrophy and tears, as well as systemic risks such as a potential increase in arteriothrombotic events like stroke and myocardial infarction.[3,5–8] Recent studies found that almost half of subjects in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) developed retinal scar in five years after initiation of anti-VEFG therapy.[9] Importantly, there are also no current treatments that can completely reverse the disease process of nAMD,[4] and studies have found persistent choroidal neovascularization exudation despite on-label dosing of current anti-VEGF-A therapies.[10,11] A recent study showed worsening vision, specifically that one third of patients' vision declined by 15 letters or more, after seven years of ranibizumab therapy.[12]

As a result of these limitations, there is a significant need for the development of novel long-acting anti-VEGF formulations as well as novel adjunctive therapies to treat nAMD (Figure 2). In particular, other members of the VEGF family are of interest, including VEGF-C and VEGF-D. Tyrosine kinase inhibitors (TKIs) are also under investigation, as they act intracellularly across VEGF receptors-1, −2, and −3, TKIs and could address upregulation

of VEGF-C and VEGF-D that occur with inhibition of VEGF-A.[13,14] The Ang-2/Tie-2 pathway has been of interest because Ang-2 has been linked to vascular leakage, abnormal blood vessel structure, and inflammation in endothelial cells.[15] Finally, integrins antagonists are being explored, as RGD-binding integrins are involved in inflammation, vascular leakage, angiogenesis, and fibrosis.[16] This review will explore the disease progression pathways of nAMD and outline current therapies and novel treatment targets for improved management of AMD.

2. Methods

A literature search was conducted through November 30, 2021 on PubMed, Medline, Google Scholar, and associated digital platforms with the following keywords: wet macular degeneration, age-related macular degeneration, therapy, VEGF-A, VEGF-C, VEGF-D, integrins, Tie2/Ang2, and tyrosine kinase inhibitors. A total of 50 papers were included in this review, nine of which were review papers. Papers were excluded if they were published before the year 2000 or if they were not written in English. The associated articles were also searched and cross-referenced for relevant citations. Information from the included studies is summarized and categorized by therapeutic target.

3. Targets for nAMD Treatment

3.1 VEGF-A ligand

Anti-VEGF-A therapy is current standard of care, however, given the limitations of this treatment, there is much interest in developing long-acting formulations to decrease the required frequency of treatment, as well as combination therapies to enhance its efficacy. Brolucizumab (Beovu, Novartis, Basel) is a humanized single-chain antibody fragment (scFv) that binds VEGF-A, with small size and high tissue penetration, which facilitates high molar concentration dosing and multi-month duration. In October 2019, the US FDA approved brolucizumab for the treatment of nAMD. However, due to events of severe vision loss related to retinal vascular occlusion and/or vasculitis, possibly secondary to inflammatory responses, in nAMD patients treated with brolucizumab, its commercial uptake has been tempered.[17]

Another sustained anti-VEGF-A delivery treatment, which has recently been FDA approved, is the ranibizumab Port Delivery System (PDS). The refillable port is a 0.05 ml reservoir that is surgically attached to the sclera and allows for continuous delivery of ranibizumab.[18] A 2021 study evaluating the PDS found that, compared to intravitreal (IVT) injections, the PDS was biocompatible and did not introduce any new toxicology-related safety concerns.[19] In May 2020, Roche announced positive Phase 3 ARCHWAY clinical trial results in nAMD, in which PDS was non-inferior to monthly ranibizumab.[20]

KSI-301 involves an antibody biopolymer conjugate (ABC) platform which maintains IVT anti-VEGF-A levels for multiple months. Specifically, KSI-301 is a humanized IgG1 antibody with a biopolymer that is an optically clear, high molecular weight phosphorylcholine polymer covalently bound by single-site specific linkage.[21] In February 2021, Kodiak Sciences announced 1-year durability, efficacy, and safety data from its

ongoing Phase 1b study of KSI-301. Two thirds of patients were able to last 6 months or longer without treatment, after 3 monthly loading doses. The Phase 2b/3 DAZZLE study is an ongoing, multi-center, randomized study that is assessing KSI-301 in patients with treatment-naïve nAMD.[22]

As another example of sustained release technology, Ocular Therapeutix is currently developing a hydrogel depot that can release drug for many months.[2] A 2019 study investigated the efficacy of anti-VEGF thermogel depots, in which anti-VEGFs were encapsulated into polyurethane thermogel depots. It was found that the anti-VEGFs could be released and stay active for up to 40 days in vitro. In rat ex vivo choroidal explants, the thermogel inhibited vessel outgrowth. Furthermore, the release rate could be modified by altering the hydrophilic/lipophilic balance.[23]

In addition to sustained delivery treatments, gene therapy with viral vectors has the potential to provide the ultimate long-term continuous expression of anti-angiogenic proteins, such as pigment epithelium derived factor, fms-like tyrosine kinase-1, ranibizumab, aflibercept, angiostatin, and endostatin.[24] Adeno-associated virus (AAV) vectors, such as adenovirus, herpes virus, and lentivirus, are especially suitable for treating ocular diseases as they only have two genes, making them straight forward to work with, and can transport large genes into RPE cells.[25] The eye is a strong candidate for gene therapy because it is easily accessible, has a tight blood-ocular barrier, and can be monitored for functional and structural outcomes non-invasively.[26] Furthermore, the ocular relative immune-privilege reduces the immune response to the genetic material that is inserted. Once the appropriate vector has been chosen and delivered via a subretinal injection, the virus may enter RPE cells or photoreceptors. These cells then transcribe and translate the genetic material into therapeutic protein. IVT injections have also been tested, however, the penetration of viral vector to the targeted tissue is thought to be inferior to subretinal delivery.[24] A three-year follow up of Phase 1 and 2a rAAV.sFLT-1 gene therapy (Avalanche Biotechnology) trial for nAMD was unable to determine the biologic efficacy of the therapy given the small sample size, but was able to confirm that it was well-tolerated among the elderly.[27]

Therapies currently under development and investigation include ADVM-022 and RGX-314 (Regenxbio).[2] ADVM-022 gene therapy utilizes a propriety vector capsid, AAV.7m8 which penetrates the internal limiting membrane when injected IVT. It carries an optimized aflibercept coding sequence and is administered as a one-time IVT therapy. ADVM-022 is an adeno-associated virus vector that encodes aflibercept. It is delivered IVT and was shown to be well-tolerated, allowing for sustained aflibercept levels in ocular tissues in a 2021 study of non-human primates.[28] AAV2-sFLT01 was evaluated in a Phase 1, open-label, dose-escalating study with 19 nAMD patients enrolled. It was found to be safe and well-tolerated at all doses.[29] RGX-314, an AAV8 vector expressing an anti-VEGF Fab, is currently being investigated in a Phase 2 clinical trial for nAMD patients via office-based subchoroidal administration, and in a Phase 3 clinical trial via subretinal administration.[30,31] Mice models have found that LV-delivered microRNAs targeting the VEGF-A gene reduced the size of laser-induced CNV 28 days after administration.[25]

There is some concern over chronic VEGF inhibition from gene therapy having negative impacts on the neurosensory retina and RPE given VEGF's potential protective effects on neuronal and glial cells.[32] Within the eye, glaucomatous optic neuropathy is a potential concern. One potential solution is for the gene therapy to regulate gene expression and protein production so that varying amounts of anti-VEGF protein are produced as opposed to continuous expression.[24]

3.2 VEGF-C and VEGF-D ligand in combination with VEGF-A ligand

With current focused VEGF-A blockage, there is a ceiling of efficacy as increased anti-VEGF-A dosage or more intense regimens yield no additional best corrected visual acuity (BCVA) benefit.[11,33,34] Anti-VEGF-A therapy has been shown to upregulate other members of the VEGF family in both macular degeneration[13] and colon cancer patients;[14] this secondary upregulation of other members of the VEGF family may account for "resistance" to VEGF-A therapy.[14]

In order to address reduced efficacy or resistance towards solely anti-VEGF-A therapy, inhibitors of other members of the VEGF family, including VEGF-C and VEGF-D, are currently being explored through combination therapy with VEGF-A. OPT-302 is a novel inhibitor of VEGF-C and VEGF-D, which are involved in angiogenesis as well as lymphangiogenesis, that prevents the ligands' binding to their endogenous receptors.[35,36] A Phase 2b clinical trial found that patients receiving 2 mg of OPT-302 in combination with 0.5 mg of ranibizumab showed superiority in visual acuity measured by BCVA from baseline to 24 weeks compared to receiving 0.5 mg of ranibizumab alone. There was a higher proportion of patients who gained 15 letter or more in the combination therapy group, as well as less subretinal and intraretinal fluid.[37]

3.3 VEGF receptors via tyrosine kinase inhibitors

Another method of inhibiting VEGF is through downstream inhibition of the tyrosine kinase cascade, which is activated when VEGF binds to its receptor. Multiple trials of tyrosine kinase inhibitors (TKIs) for the treatment of nAMD are underway. By acting intracellularly across VEGF receptors-1, −2, and −3, TKIs could address upregulation of VEGF-C and VEGF-D that occur with inhibition of VEGF-A.[13,14] One multitargeted tyrosine kinase inhibitor (TKI) currently in development is GB-102 (GrayBug Vision), containing Sunitinib maleate. Its method of delivery is sustained release via an injectable depot designed for twice per year formulation. Administered IVT, GB-102 gradually biodegrades and blocks angiogenesis. A major advantage of this approach is its sustained release, allowing for increased time in between treatments and potentially easier treatment adherence for patients.[38] SU11248, Sunitib, administered orally was shown to suppress choroidal neovascularization (CNV) in a 2006 study conducted in mice.[39] Sunitinib malate was also investigated in vitro via encapsulation in poly(lactic-co-glycolic acid) nanoparticles then incorporated into a thermo-reversible gel formation for sustained release.[40] This gel showed higher uptake, better anti-angiogenic potential, and longer inhibition of VEGF compared with plain drug solution.[40] Sunitinib has also been studied in the form of microparticles, which were shown to self-aggregate into a depot and effectively suppressed CNV in mice for six months, which indicates another potentially long-acting therapy for

nAMD.[41] GrayBug Vision completed its Phase2b ALTISSIMO trial in nAMD in January of 2021 (NCT03953079).[42] Control of central sub-field thickness (CST) in patients treated with GB-102 1mg twice per year was similar to bi-monthly aflibercept when compared with baseline. However, BCVA was lower in GB-102 1mg patients as compared with aflibercept.[43]

Another sustained delivery therapy is EYP-1901, an erodible Durasert® sustained released technology containing vorolanib (EyePoint Pharmaceuticals). Vorolanib is a small molecule TKI with inhibitory activity against all isoforms of VEGF and PDGF which has shown biologic signs of effect when previously assessed as an oral formulation in nAMD patients. A Phase 1/2a study is currently underway.[44] Preliminary results from the Phase 1 trial were presented at the 2021 American Academy of Ophthalmology Conference, which reported no ocular or drug-related serious adverse events. Specifically, there were no observed cases of vitreous floaters, endophthalmitis, retinal detachment, implant migration in the anterior chamber, retinal vasculitis, or posterior segment inflammation.[45]

Axitinib is a small molecule multi-receptor tyrosine kinase inhibitor that is being developed by multiple companies including Clearside Biomedical Inc. and Ocular Therapeutix.[46] Axitinib is currently used to treat advanced renal cell carcinoma, but it has potential for treating nAMD as a potent TKI. A 2016 study conducted by Giddabasappa and colleagues found that axitinib's panVEGF inhibition and PDGF inhibition allowed it to inhibit neovascularization better than anti-VEGF or anti-h-PDGF-B mAb in in vitro models.[47] A suprachoroidal injection of axitinib in rabbits showed an 11-fold higher mean axitinib exposure in the posterior eye cup, compared to the IVT injection. The retinal pigment epithelium-choroid-sclera (RCS) and retina also showed sustained levels of axitinib throughout the study after a single suprachoroidal injection.[46] These results demonstrate the favorable pharmacokinetic properties of suprachoroidal axitinib delivery with long-acting potential that could reduce treatment burden to nAMD patients.

Suprachoroidally injected axitinib (CLS-AX) has been assessed in an ongoing Phase 1/2a clinical trial (OASIS, NCT04626128) in six patients with nAMD (Cohort 1). The lowest planned dose of 0.03 mg CLS-AX was found to be well tolerated in patients and no serious adverse events were observed. One month after receiving standard-of-care, single intravitreal injection of 2 mg aflibercept, the mean Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA score for all six patients remained stable, changing only by −0.2 letters, which is approximately the same rate of change for patients on standard anti-VEGF-A therapies.[48] Patients then received a single suprachoroidal dose of 0.03 mg CLS-AX and showed a mean ETDRS BCVA improvement of +4.7 letters (p=0.029, post hoc, unadjusted) one month later. The trial has advanced to Cohort 2, using a dose of 0.1 mg CLS-AX.[49]

In February 2021, Ocular Therapeutix presented data from its Phase 1 clinical trial of OTX-TKI, an axitinib intravitreal implant for nAMD, which demonstrated its favorable safety profile with no serious ocular adverse effects across the first two dose cohorts and a portion of the third dose cohort for up to six months or longer.[50] Durability of treatment and Maximum Tolerated Dose (MTD) will need to be determined through long-term evaluation of both cohorts in the ongoing study.[51]

3.4 Tie/Ang 2

The angiopoeitins, Ang-1 and Ang-2, which are growth factors that bind to the Tie-2 tyrosine kinase receptor, have been a recent target of interest for retinal vascular diseases such as nAMD. Tie-2 is expressed on endothelial cells, and Ang-1 and Ang-2 are both growth factors that are involved in angiogenesis and vascular permeability.[52] The Ang-2/Tie-2 pathway has been of particular interest because Ang-2 has been linked to vascular leakage, abnormal blood vessel structure, and inflammation in endothelial cells. When Ang-2 is upregulated, pathological neovascularization and increased vascular permeability can occur.[52] Therefore, drugs that inhibit the Ang-2 may be suitable for treating nAMD.

Combination therapy of anti-VEGF-A with Ang-2 inhibition has been shown to be superior to anti-VEGF-A monotherapy as indicated by more effectively reduced vessel lesion number, permeability, retinal edema, and neuron loss compared to either therapy alone.[53] Faricimab is a novel bispecific antibody that binds to both VEGF-A and Ang-2 designed for IVT use. In January 2021, Roche announced that two global Phase III studies of faricimab in nAMD met their primary endpoint and showed potential to extend time between treatments up to 16 weeks. Faricimab showed potential to extend time between treatments up to 16 weeks in approximately half of the research subjects with non-inferior gains in visual acuity compared to aflibercept administered every eight weeks.[54]

AXT-107 (AsclepiX Therapeutics, NJ) is a collagen IV-derived peptide that disrupts α5β1 integrins, activates Tie-2, and inhibits both VEGF-A and VEGF-C. With a long half-life and IVT gel depot formation, AXT107 has the potential to be dosed yearly, based on preclinical studies.[55] Given its promising mechanism of action, AXT107 is currently being evaluated for its safety and bioactivity for nAMD in Phase 1/2a clinical trials.[55] Another molecule being studied for its interaction in the Tie2/Ang2 pathway is AKB-9778, a small-molecule inhibitor of vascular endothelial-protein tyrosine phosphatase. A 2014 study found that AKB-9778 induced phosphorylation of Tie2 and suppressed neovascularization and VEGF-induced vascular leakage in the retina and choroid, making it a potential treatment for vascular eye diseases such as nAMD and diabetic retinopathy.[56]

Another factor in the Tie2/Ang2 pathway that has been studied is Tie2-expressing macrophages (TEM), which exist in the peripheral blood, bone marrow, and some tumors.. Zhang and colleagues examined the mechanism of TEMs in angiogenesis using macrophage-specific Tie2 knockout mice with laser-induced CNV and found that TEMs mediate autophagy and neovascularization.[57] Though the exact mechanism of how TEMs are involved in the pathogenesis of AMD are unknown, the results suggest that TEMs may be a novel preventive target for the treatment of AMD.

One studied examined angiopoetin-like protein 2 (Angptl2), a cytokine that does not bind to Tie-1 or −2, suggesting that it has a different function than angiopoietin, though the underlying mechanisms are still unknown. Angptl2 is involved in age-related systemic diseases and has been suggested to be a multistep regulator of CNV pathogenesis.[58] Hirasawa and colleagues examined the role of Angptl2 in CNV development using a murine model of laser-induced CNV, which possesses similarities to AMD, and found that Angptl2 deficient mice exhibited suppressed CNV development, leading to reduced macrophage

infiltration and inflammatory response.[58] These results suggest that inhibiting Angptl2 may be a promising new therapy for AMD treatments, especially for patients who do not respond to the current standard of AMD therapy.

3.5 Integrins

Integrin receptors are heterodimeric adhesion proteins that reside within the membrane and play a key role in connecting the extracellular and intracellular environments.[59] Recently, there has been interest in targeting integrins, specifically arginyl-glycyl-aspartic acid (RGD)-binding integrins as these are expressed in the tissues of the eye. These RGD-binding integrins are involved in inflammation, vascular leakage, angiogenesis, and fibrosis. High levels of αvβ3 integrin were found in human neovascular choroidal membranes, making them intriguing targets for vascular diseases of the eye, including nAMD.[16]

One study examined a novel pan RGD (arginylglycylaspartic acid) integrin receptor antagonist, THR-687, that competes for binding with the integrin receptor's natural ligand.[60] THR-687 prevented the migration of human umbilical vein endothelial cells and induced regression of pre-existing vascular sprouts.[60] These results suggest that THR-687 may be a promising antagonist for use in treating nAMD as well as other retinal vascular eye diseases such as diabetic retinopathy. Another drug being investigated is risuteganib (Allegro Ophthalmics), a novel anti-integrin peptide. A Phase 1b study gave three monthly IVT injections of the drug to 15 nAMD subjects. These injections were well tolerated and showed improvement in visual acuity as well as a decline in central macular thickness.[61]

SF0166 is a αvβ3 antagonist that has been studied for nAMD treatment as topical ocular drug. A soluble masked Phase 1/2 study 42 in nAMD patients showed clinically significant therapeutic effects in nine of the 42 patients. No drug-related serious adverse events were observed in the 28-day study period or in the 28-day follow up.[62] There are also a number of IVT α5β1 inhibitors, including volociximab (Ophthotech) and JSM6427 (Jerini Ophthalmic, currently Takeda Pharmaceutical Company) being studied in Phase 1, open label, dose escalation studies.[59] Wang and colleagues examined the effect of ATN-161, an α5β1 inhibitor, delivered in combination with anti-VEGF monoclonal antibody in rats with laser-induced CNV and found that the dual inhibition of integrin α5β1 and VEGF jointly inhibited angiogenesis.[63]

While integrin inhibitors are a promising therapeutic target for nAMD, their functions are complex and context-dependent, therefore, more research and development are needed to better understand the underlying cellular mechanisms.[59] It is also possible that combination therapies of VEGF and integrin inhibitors may be possible and have synergistic multi-pathway benefits for patients, representing an area of future research.

4. Conclusion:

The current gold standard of anti-VEGF-A monotherapy does not adequately address the complex, multifactorial pathogenesis of nAMD. Significant limitations of anti-VEGF based therapies include access and need for frequent injections and high cost. Numerous novel therapies are currently in development to address the shortcomings of VEGF-A inhibitors,

including new targets as well as unique delivery mechanisms. Recent clinical trials have shown promising results for therapies targeting integrins, tyrosine kinase inhibitors, the Tie2/Ang2 pathway, and VEGF-C and VEGF-D. Furthermore, new sustained-release delivery mechanisms such as surgically placed ports, thermogels, and gene therapy represent promising ways to reduce the need for frequent injections and reduce treatment burden on patients with AMD.

EXPERT OPINION:

Neovascular AMD is the leading cause of irreversible blindness in developed countries. It is characterized by the growth of pathologic neovascularization beneath the macula, which leads to exudation of blood and/or fluid into the macula, followed by destructive macular scar and central blindness. CNV growth is driven by upregulation of the pro-angiogenic cytokine, VEGF-A. Current anti-VEGF therapies for nAMD, including bevacizumab, ranibizumab, and aflibercept, have certainly lowered the incidence of blindness and reduced severe vision loss in countless patients. However, due to the persistent elaboration of VEGF-A in nAMD, coupled with the limited durability of current therapies, frequent administration is required, leading to significant treatment burden. It has been shown that real world nAMD patients receive fewer injections of anti-VEGF and experience inferior visual outcomes compared to patients enrolled in randomized controlled trials, who receive fixed, frequent therapy. Importantly, older adults whom are at the highest risk for AMD progression are specifically prone to undertreatment. Differences in visual acuity gains between real world and clinical trials is likely due to lack of patient adherence to the injection schedule, infrequent treatment monitoring, costs, and incomplete treatment. There is also concern that repeated injections can increase risk of ocular complications, including ocular hypertension and retinal tears, and systemic risks, such as stroke, myocardial infarction. Determining how to lower this risk of ocular complications is imperative for future clinical success. In addition to novel therapeutic targets, there is significant need for earlier detection and prevention capabilities in the management of AMD.

Novel therapies currently in development show promise in addressing a number of traditional AMD treatment shortcomings. First, sustained-delivery systems described in this review, such as the ranibizumab PDS, Durasert® Bioerodible TKI, ENV1305, Vitrasert, Retisert, and hydrogel anti-VEGF depot, are designed to last for at least six months, enhancing durability, reducing the number of times a patient needs to see their physician for treatment, and increasing adherence to the therapy. Second, broad VEGF inhibition and targeting novel ligands such as integrins, tyrosine kinase inhibitors, and Tie2/Ang2 have the potential to have enhanced effectiveness over anti-VEGF-A therapies. In addition, these novel therapies can be used in combination with anti-VEGF-A for potentially superior efficacy. Lastly, gene therapy to create therapeutic protein “biofactories” for continuous anti-VEGF-A expression may be the ultimate long-lasting treatment that could eliminate the need for injections permanently.

Key considerations in the development of novel AMD therapies include safety, efficacy, cost, accessibility to patients, and consideration is how the therapies differ in treatment-naïve patients compared to those who have already received anti-VEGF-A therapy. All data

point to the importance of establishing a regular treatment schedule as opposed to as-needed injections, as the former leads to better treatment adherence and visual outcomes.

Given that some new AMD therapies have only been tested in animal models, the next step is to progress to clinical trials and test for efficacy in humans. For those therapies that have been tested in human populations, further testing on larger sample sizes across various population groups is critical. Early clinical trials of many of these new therapies outlined in this review have shown that the novel drug is well-tolerated and safe, however these trials were conducted on a small sample size. Other trials have also shown non-inferiority of the new treatment compared to the standard of care. However, superiority over the current standard of treatment has yet to be widely established and represents a crucial gap in our current scientific understanding of these new drug targets. As a result, before these novel therapies can the new gold standard for treating AMD, testing in larger and more diverse samples should be the primary goal of researchers in the field. A key challenge will be comparing new therapies to current anti-VEGF through head-to-head testing in large, longitudinally observed populations in a real-world setting to eliminate bias compared to strict treatment adherence observed in controlled clinical trials. Once these longitudinal clinical trials have been conducted, only then will we be able to understand these novel targets' therapeutic potential.

In summary, although anti-VEGF-A therapies have revolutionized treatment for nAMD, significant unmet need persists to address limited visual outcomes and treatment burden. Given the encouraging results in early clinical trials, the future is hopeful for patients afflicted with nAMD, the leading causes of vision loss in the industrialized world.

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Article highlights:

- VEGF-A is the current target of treatment for nAMD, and standard of care currently involves anti-VEGF-A monotherapy, specifically aflibercept, bevacizumab, and ranibizumab.
- The current standard of care has many limitations, including a ceiling of efficacy, the need for frequent injections, high costs, incomplete treatment schedules, and reduced real-world efficacy.
- Novel treatments in development for AMD include targets of VEGF-C and VEGF-D, integrins, tyrosine kinase inhibitors, and the Tie2/Angiopoetin-2 pathway, as well as combination therapy and gene therapy.
- OPT-302, a novel inhibitor of VEGF-C and VEGF-D, is one of the first to find superiority in visual acuity with combination therapy over ranibizumab monotherapy, as indicated by results from a Phase 2b clinical trial.
- Multiple early clinical trials of novel targets show promising safety profiles and non-inferiority, however, further longitudinal trials comparing new targets to the current standard of care are needed to establish superiority of treatment.

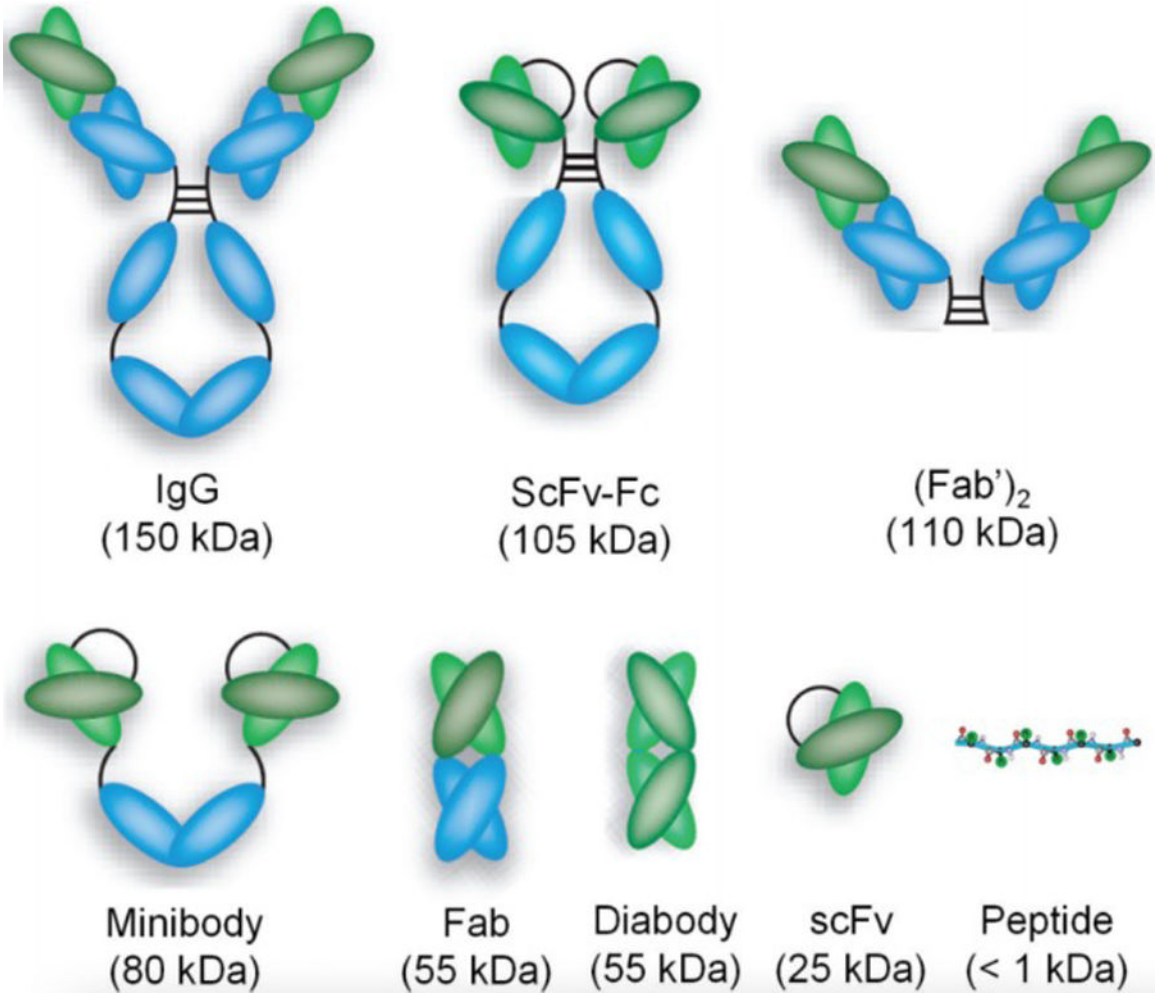

Figure 1:

Intact antibodies and a variety of antibody fragments. This figure allows one to compare the sizes of various AMD antibody drugs. Bevacizumab is a humanized immunoglobulin G monoclonal antibody (149 kDa) whereas Ranibizumab is an antibody fragment (38 kDa) and Brolucizumab is a single chain antibody fragment (26 kDa). Attribution: Hao Hong, Jiangtao Sun and Weibo Cai, CC BY 3.0 <https://creativecommons.org/licenses/by/3.0>, via Wikimedia Commons.

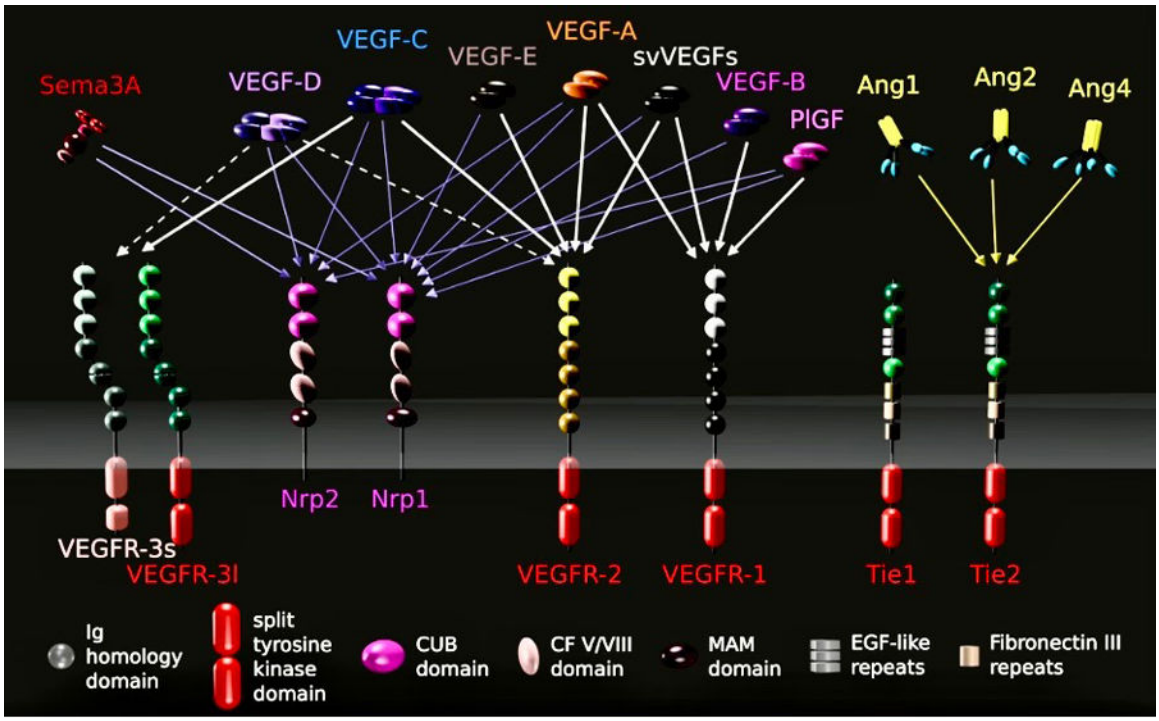

Figure 2:

This image shows various novel targets of new AMD therapies, including VEGF-C, VEGF-D, and Tie/Ang2. Edited from: **Attribution**: mjeltsch, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons.