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PERSPECTIVE

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. Current standard-of-care anti-vascular endothelial growth factor (VEGF) therapy, which inhibits angiogenesis and vascular permeability, has been shown to stabilize choroidal neovascularization and increase visual acuity in neovascular AMD. However, therapeutic limitations of anti-VEGF therapy include limited durability with consequent need for frequent intravitreal injections, and a ceiling of efficacy. Current strategies under investigation include targeting VEGF-C and VEGF-D, integrins, tyrosine kinase receptors, and the Tie2/angiopoietin-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, there is potential to address treatment burden and to improve outcomes for patients afflicted with neovascular AMD.

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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 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 (PIGF), 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 primary target of treatment for nAMD, and standard of care currently involves anti-VEGF-A intravitreal (IVT) injection monotherapy specifically aflibercept (which also binds PIGF), off-label bevacizumab, and ranibizumab (Figure 1).

These current VEGF therapies, however, possess several limitations. First, current 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 [2,3]. Second, the injections cause patient anxiety and discomfort [4]. Furthermore, there are potential ocular risks associated with repeat injections, including sustained ocular hypertension, endophthalmitis, and retinal tears and detachment, 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 5 years after initiation of anti-VEGF therapy [9]. Importantly, no current treatments 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 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

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Article highlights

- VEGF-A is the current primary target of treatment for nAMD, and standard of care currently involves IVT anti-VEGF-A monotherapy, specifically ranibizumab, aflibercept (which also binds PlGF), and off-label bevacizumab. Brolucizumab is another anti-VEGF-A IVT therapy that was more recently approved in 2019.
- The current standard of care has limitations, including a ceiling of efficacy, the need for frequent IVT injections, high costs for approved anti-VEGF therapies, and reduced real-world outcomes, likely related to treatment burden.
- Novel treatments in development for nAMD target VEGF-C and VEGF-D, integrins, tyrosine kinase receptors, and the Tie2/angiopoetin-2 pathway, as well as combination therapy and gene therapy biofactory strategies. Early clinical trials show promising safety profiles and biologic effect; further clinical study is waranted.
- The October 2021 FDA approval of the ranibizumab port delivery system and the January 2022 FDA approval of Faricimab potentially introduce new standards for durability in the treatment of nAMD.

VEGF receptors-1, -2, and -3, 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, integrin antagonists are being explored, as RGD (arginyl-glycyl-aspartic acid; Arg-Gly-Asp) binding integrins are involved in inflammation, vascular leakage, angiogenesis, and fibrosis [16]. This review will explore the disease progression pathways of nAMD and novel treatment targets for improved management of AMD. It is not meant to provide an exhaustive discussion of latest clinical trial results, but instead highlights some clinical evidence that supports the role of these novel treatment targets.

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 47 papers were included in this review, 14 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, Figure 1) that binds VEGF-A, with small size and high tissue

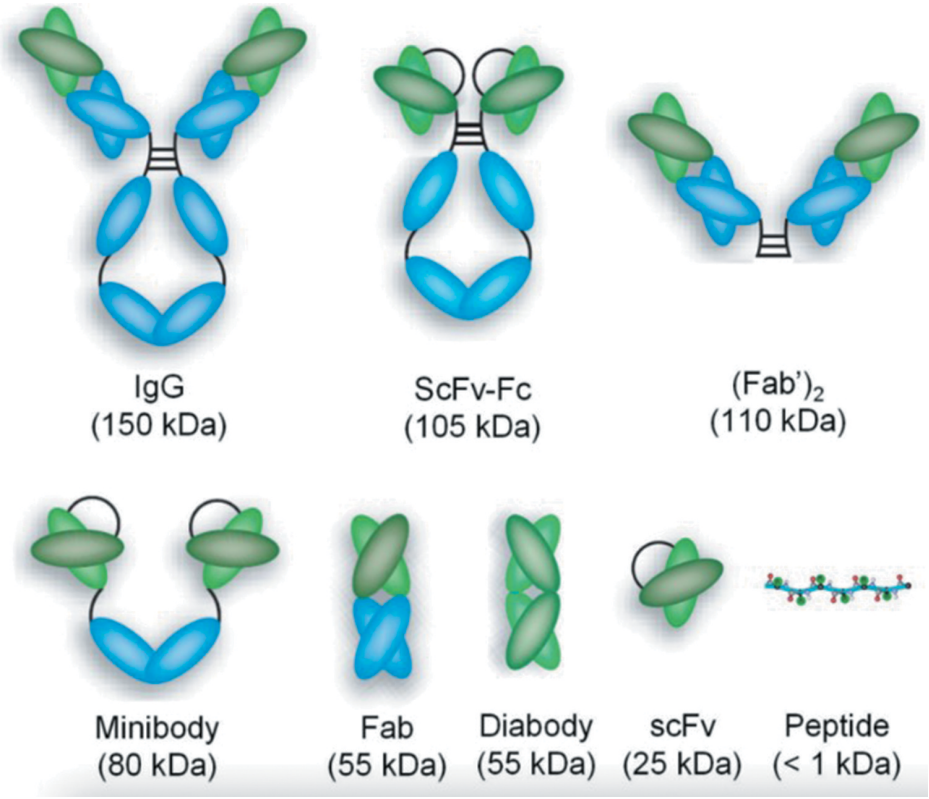

Figure 1. Intact antibodies and a variety of therapeutic antibody fragments. Bevacizumab is a humanized immunoglobulin G monoclonal antibody (IgG, 149 kDa) whereas Ranibizumab is an antibody fragment (Fab, 48 kDa) and Brolucizumab is a single chain antibody fragment (scFv, 26 kDa). For comparison, aflibercept (115 kDa) is a recombinant fusion protein consisting of key binding portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG. Attribution: Hao Hong, Jiangtao Sun and Weibo Cai, CC BY 3.0 <https://creativecommons.org/licenses/by/3.0>, via Wikimedia Commons.

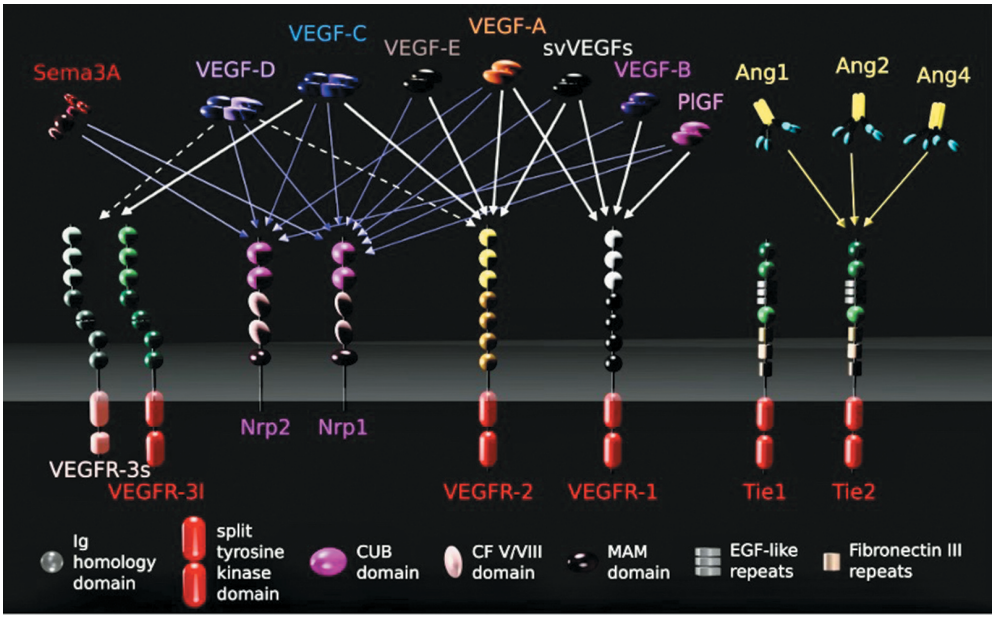

Figure 2. This image shows various novel targets of investigational AMD therapies, including VEGF-C, VEGF-D, and Tie/Ang2. Edited from: **Attribution**: mjeltsch, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia commons.

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 surgically attached to the sclera and allows for continuous delivery of ranibizumab [18]. A 2021 study evaluating the PDS found that, compared to IVT, 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, multicenter, 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 biological effect 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, are especially suitable for treating ocular diseases as they only have two genes, making them straightforward to work with and show low inflammatory potential, as well as nonintegrating nature with a favorable safety record [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, it 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 3-year follow-up of Phase 1 and 2a rAAV.sFLT-1 subretinal 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 (Adverum Biotechnologies) 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. It was shown to be well tolerated, allowing for sustained aflibercept levels in ocular tissues in a 2021 study of non-human primates [28]. Recently presented results from the OPTIC study of ADVM-022 in nAMD demonstrated sustained durability and a promising safety profile in nAMD patients who previously required frequent anti-VEGF injections [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].

There is some concern over chronic VEGF inhibition from gene therapy, with possible 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 to focused 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 letters 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 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 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, with potential to address treatment burden [38]. SU11248, sunitinib, 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 6 months, suggesting potential as a long-acting therapy for nAMD [41]. GrayBug Vision completed its Phase2b ALTISSIMO trial in nAMD in January 2021[42]. Control of central subfield thickness (CST) in patients treated with GB-102 1 mg twice per year was similar to bi-monthly aflibercept when compared with baseline. However, BCVA trended lower in GB-102 1 mg patients as compared with aflibercept, with high standard deviation driven by 6 patients [43].

Another sustained delivery TKI 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, and 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 TKI 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 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. The trial has advanced to Cohort 2, using a dose of 0.1 mg CLS-AX [48].

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 6 months or longer [49]. Durability of treatment and Maximum Tolerated Dose (MTD) will need to be determined through long-term evaluation in the ongoing study [50].

3.4. Tie/Ang 2

The angiopoeitins, Ang-1 and Ang-2, 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 modulates vascular stability [15]. The Ang-2/Tie-2 pathway has been of particular interest because Ang-2 binding to Tie-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 [15]. 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 [51]. Faricimab is a novel IVT bispecific antibody that binds to both VEGF-A and Ang-2. In January 2021, Roche announced that two global Phase 3 studies of faricimab in nAMD met their primary endpoint. 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 8 weeks [52].

AXT-107 (AsclepiX Therapeutics, NJ) is a collagen IV-derived peptide that disrupts α5β1 integrins, activates Tie-2, and inhibits VEGF receptor 2. With a long half-life and IVT gel depot formation, AXT107 has the potential to be dosed yearly, based on preclinical studies [53]. Given its promising mechanism of action, AXT107 is currently being evaluated for its safety and bioactivity for nAMD in Phase 1/2a clinical trials [53]. 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 [54].

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 [55]. Although the exact mechanism of how TEMs are involved in the pathogenesis of AMD is unknown, the results suggest that TEMs may be a novel preventive target for the treatment of AMD.

One study 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 [56]. 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 [56]. 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 [57]. Recently, there has been interest in targeting integrins, specifically 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 integrin receptor antagonist, THR-687, that competes for binding with the integrin receptor's natural ligand [58]. THR-687 prevented the migration of human umbilical vein endothelial cells and induced regression of preexisting vascular sprouts [58]. 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. It has shown promise in early studies of diabetic macular edema and non-neovascular AMD. A Phase 1b study administered 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, however, follow up studies in nAMD have not been announced [59].

SF0166 is a αvβ3 antagonist that has been studied for nAMD treatment as topical ocular drug. A double masked Phase 1/2 study 42 in nAMD patients showed biologic 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 [60]. There are also a number of IVT α5β1 inhibitors, including volociximab (Ophthotech) and JSM6427 (Jerini Ophthalmic, currently Takeda Pharmaceutical Company) that have been studied in Phase 1, open label, dose escalation studies [57]. 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 [61].

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 [57]. It is also possible that combination therapies of VEGF and integrin inhibitors may have synergistic multi-pathway benefits for patients, representing an area of future research.

4. Conclusion

The current gold standard of anti-VEGF-A IVT monotherapy does not completely address the complex, multifactorial pathogenesis of nAMD. Meaningful limitations of anti-VEGF-based therapies include limited durabilty with consequent need for frequent injections, a ceiling of efficacy, and high cost for approved therapies. Numerous novel therapies are currently in development to address these limitations, and involve new targets as well as unique delivery mechanisms. Recent clinical trials have shown promising results for therapies targeting integrins, tyrosine kinase receptors, the Tie2/Ang2 pathway, and VEGF-C and VEGF-D. Furthermore, new sustained-release delivery technologies such as surgically placed ports, thermogels, and gene therapy may reduce the need for frequent injections and reduce treatment burden on patients with AMD.

5. 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 IVT 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 meaningful 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 are likely due to lack of patient adherence to the injection schedule. There is also concern that repeated injections can increase risk of ocular complications, including endophthalmitis, ocular hypertension and retinal tears. In addition to the need for more durable treatments, there is unmet need for greater efficacy 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 may reduce the number of treatments and increase adherence to the therapy. Of note, the ranibizumab PDS received FDA approval in October 2021 for the treatment of nAMD and offers a promising alternative to frequent injections. Second, broad VEGF inhibition and novel targets such as integrins, tyrosine kinase receptors, 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. The January 2022 FDA approval of faricimab for the treatment of nAMD as well as DME may represent an important step forward as it is the first bispecific antibody, targeting both VEGF-A and Ang-2, to be approved for treatment of ocular diseases. Lastly, gene therapy to create therapeutic protein 'biofactories' for continuous anti-VEGF-A expression may represent the ultimate long-lasting treatment that could dramatically reduce treatment burden.

Key considerations in the development of novel AMD therapies include safety, efficacy, route of administration and durability. In addition, costs and real world outcomes are becoming increasingly important to providers and payors. The October 2021 FDA approval of the ranibizumab port delivery system and the January 2022 FDA approval of Faricimab potentially introduce new standards for durability in the treatment of nAMD. In the future, choice of active comparator in randomized controlled clinical trials will become more complex as additional approved therapies are introduced.

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

Declaration of interests

A Harris would like to disclose that he received remuneration from AdOM, Qlaris, Luseed, and Cipla for serving as a consultant, and he serves on the board of AdOM, Qlaris, and Phileas Pharma. Alon Harris holds an ownership interest in AdOM, Luseed, Oxymap, Qlaris, Phileas Pharma, SlitLed and QuLent. All relationships listed above are pursuant to Icahn School of Medicine's policy on outside activities. T Ciulla would like to disclose that he receives salary from Clearside Biomedical and he holds equity in Clearside Biomedical. This work was undertaken in his role as a Volunteer Clinical Professor at Indiana University School of Medicine and does notreflect any views or opinions of this corporation or its management. The contribution of the author Francesco Oddone was supported by Fondazione Roma and by the Italian Ministry of Health. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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