New Treatment Modalities for Neovascular Age-Related Macular Degeneration

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Abstract: Age-related macular degeneration (AMD) is considered one of the main causes of severe vision loss in older adults. The neovascular form (nAMD) is an advanced stage, which is responsible for the most severe vision loss. Vascular endothelial growth factor (VEGF) is at present the main factor that leads to the development of a neovascular membrane and the increased leakage from the membrane to the retina. At present, anti-VEGF therapy is the only treatment that achieves vision gains in many patients and halts progression in most of them. VEGF blockade can be achieved with several molecules and various treatment regimens, which have been studied with excellent results. Unfortunately, real-world data has shown to be far less efficacious than clinical trials. This gap between clinical trials and real-world results is an unmet medical need that supports the necessity of new treatment modalities for nAMD. Of the various treatments being studied, anti-VEGFs of higher efficacy and longer durability are those more advanced in their development. Brolucizumab and abicipar pegol are 2 new anti-VEGF drugs that had positive results in phase 2 studies and are being tested in phase 3 trials at present. Other promising therapies are antiangiopoietin 2 molecules, which are in phase 2 development. At earlier stages of development but with promising results are squalamine, anti–VEGF-C and -D, and gene therapy. The future will give retina specialists a broad armamentarium with which patients may achieve high visual gains for the long term with a low treatment burden.

Key Words: neovascular, AMD, new, treatment, VEGF

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Age-related macular degeneration (AMD) is described as the most frequent cause of uncorrectable severe vision loss in people older than 55 years of age in the developed world. As many as 30% of adults 75 years of age or older develop signs of senile retinal degeneration, and the prevalence of AMD is increasing due to an aging population.[1,2]

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Choroidal neovascularization (CNV) due to neovascular AMD (nAMD) is responsible for most AMD-related severe vision loss. Anti–vascular endothelial growth factor (anti-VEGF) agents, delivered intravitreally, block the angiogenic process, the growth of abnormal blood vessels in the eye, to prevent loss of vision and, in some cases, improve vision.[3]

Over the past decade, the only effective treatments that prevented vision loss in most patients were anti-VEGF agents.[4] These agents reduce the growth of new blood vessels from existing blood vessels by blocking the activity of the essential positive regulatory factor, VEGF. The result of the action of the VEGF molecule inducing growth of new vessels is known as angiogenesis.

Angiogenesis is a multistep, tightly regulated process that is controlled by a dynamic balance of positive and negative factors.[5] Factors that induce angiogenesis are VEGF, angiopoietins, fibroblast growth factors, transforming growth factor-alpha and -beta, hepatocyte growth factor, interleukin-8, and connective tissue growth factor. Those that inhibit or modulate angiogenesis are vasostatin, angiostatin, endostatin, plasminogen kringle 5, thrombospondin, and pigment epithelium derived factor.[6,7]

The large family of VEGF molecules includes VEGF-A, -B, -C, -D, and -E and placental growth factor (PlGF). It is believed the main type responsible for angiogenesis is VEGF-A, interacting with VEGF receptor (VEGFR) 1 and 2. Other types of VEGF play different roles and do not directly stimulate angiogenesis or changes in permeability.[8]

Several agents manage at present to modulate angiogenesis/permeability by blocking VEGF and preserving or improving vision in most patients. The first drug to be approved that showed gains in vision of patients affected by neovascular AMD was ranibizumab. The ANCHOR and MARINA trials were the pivotal studies that compared the use of ranibizumab versus photodynamic therapy in classic membranes (ANCHOR) and versus placebo in occult membranes (MARINA), yielding vision gains for the ranibizumab groups and vision loss in the comparator groups.[9,10] Another drug that showed efficacy initially when used systemically and then intravitreally was bevacizumab. Although never approved for this specific indication, the drug was used as an off-label treatment for neovascular AMD.[11,12]

Later in 2012, aflibercept, a fusion protein, was approved for the treatment of neovascular AMD based on the results of the VIEW 1 and 2 trials.[13] This drug showed a similar efficacy and was noninferior to ranibizumab. Conbercept is another anti-VEGF agent that has been successfully used to treat neovascular AMD, but it is only approved for use and available in China.[14] The oncology formulation of aflibercept, ziv-aflibercept, has also been used successfully to treat nAMD patients, although its use is off-label, similar to bevacizumab but less widespread.[15] All these agents have different costs and access levels depending on whether they are licensed, but there is comparable efficacy

among them.[4,13]

Despite having drugs that achieve positive results in clinical trials, with varying results according to the different treatment strategies, real-world results have been disappointing in several reports, even from countries with good medical access.[16] Long-term follow-up of patients enrolled in clinical trials using anti-VEGF for neovascular AMD also showed poor results after 5 years of treatment.[17] The main reason for low visual gains is linked to reduced frequency of injections and increased time between visits. These long-term clinical trial results tend to be similar to real-world settings.[18] It has been speculated that long-term results could have been better at a cost of heavy burdens to the health system and patients alike.

At present neovascular AMD treatment has very positive results in clinical trials and less successful results in real life. All treatments available today have the same or very similar mechanism of action, which is blockade of the VEGF molecule.

NEED FOR NEW TREATMENT MODALITIES

Newer treatment strategies (Table 1) are needed to close the gap between clinical trial results and real-world settings. These new treatment modalities should be able to have better efficacy, longer duration of action, or simultaneous effects on angiogenesis/permeability and the main physiopathologic cause for poor long-term results: atrophy and scarring.[19,20]

EARLY DETECTION AND PREVENTION

Although there are currently no proven effective treatments for early AMD, the next and emerging frontier for AMD treatment development is targeted at early AMD. Within this context, early detection of AMD will be beneficial for the individual and public health. Ophthalmologists whose practices focus on primary care will ultimately be at the center of this process, tasked with the responsibility of early AMD detection in the increasing numbers of older eyes at risk for AMD.

Intermediate AMD, according to the Age-Related Eye Disease Study classification, may have a risk of progression to advanced AMD of up to 50% in 5 years. Closer follow-up of patients at risk would allow for early treatment and better visual outcomes.[21,22]

Additionally, there is a large volume of evidence supporting the use of vitamin and mineral supplementation for delaying progression of AMD. This evidence has been largely drawn from a study with long follow-up in a well-nourished American population, which may limit the generalizability of the results to other populations.[23]

There is a strong association between the risk of both geographic atrophy and CNV and pack years of cigarette smoking, supporting a causal relation between smoking and AMD. Smoking cessation may have a strong impact on AMD progression.[24] It is not clear though, whether once a neovascular stage has been reached, quitting smoking has an impact on the number of injections or visual gain.

NEW ANTI-VEGF MOLECULES

Brolucizumab (RTH258, formerly ESBA1008, Alcon) is a humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A. It is the smallest of the anti-VEGF antibodies, with a molecular weight of 26 kDa, compared with 115 kDa for aflibercept and 48 kDa for ranibizumab. By virtue of its design, it is possible to concentrate brolucizumab up to 120 mg/mL, allowing the administration of 6 mg in a single 50-mL intravitreal injection. On a molar basis, 6 mg of brolucizumab equals approximately 12 times the 2.0-mg dose of aflibercept and 22 times the 0.5-mg dose of ranibizumab. These attributes may confer potential advantages in the treatment of nAMD. A small molecular weight and high drug concentration gradient between the vitreous and retina may support drug distribution into the retina. Assuming comparable half-life, higher molar doses of drug may be cleared more slowly from the eye, thus prolonging duration of action.

In a phase 2 noninferiority study between aflibercept and brolucizumab, participants were randomized 1:1 to intravitreal brolucizumab (6 mg/0.05 mL) or aflibercept (2 mg/0.05 mL). Both groups received 3 monthly loading doses and were then treated every 8 weeks (q8) with assessment up to week 40. In the brolucizumab group, the final q8 cycle was extended to enable 2 cycles of treatment every 12 weeks (q12; to week 56); participants on aflibercept continued on q8. Unscheduled treatments were allowed at the investigator's discretion.

This study found that the mean best-corrected visual acuity (BCVA) change from baseline (letters) with brolucizumab was noninferior to aflibercept at week 12 [5.75 and 6.89, respectively (80% confidence interval for treatment difference, 4.19 to 1.93)]

TABLE 1. Treatments for Neovascular AMD

Target	Drug Name	Company	Stage of Development	Results
VEGF	Brolucizumab	Novartis	Phase 3	Positive first year
VEGF	Abicipar pegol	Allergan	Phase 3	Ongoing
Angiopoietin 2	RG7716	Roche	Phase 2	Ongoing
Angiopoietin 2	Nesvacumab	Regeneron	Phase 2	Ongoing
siRNA	Bevasiranib	Opko	Phase 3	Trial stopped
VEGF downstream	Squalamine, OHR-102	Ohr Pharmaceutical	Phase 3	Ongoing
PDGF	Pegpleranib (Fovista)	Ophthotech	Phase 3	Negative
PDGF	Rinucumab	Regeneron	Phase 2	Negative
VEGF-C and -D	OPT-302	Ophthea	Phase 1	Positive
VEGF PlGF	sFLT-1 (rAAV- intravitreal gene therapy)	Genzyme Sanofi	Phase 1	Positive
VEGF	Port delivery system	ForSight VISION4	Phase 2	Ongoing

and week 16 [6.04 and 6.62 (3.72 to 2.56)], with no notable differences up to week 40.

Outcomes exploring disease activity during the q8 treatment cycles suggest greater stability of the brolucizumab participants, supported by receipt of fewer unscheduled treatments versus aflibercept (6 vs 15) and more stable central subfield foveal thickness reductions. In addition, from post hoc analysis, a greater proportion of brolucizumab-treated eyes had resolved intraretinal and subretinal fluid compared with aflibercept-treated eyes. Approximately 50% of brolucizumab-treated eyes had stable BCVA during the 12 weekly cycles. It was also described that brolucizumab and aflibercept adverse events were comparable.[25]

Based on these positive phase 2 results, 2 phase 3 trials, HAWK and HARRIER, were initiated. HAWK and HARRIER (NCT02307682 and NCT02434328) are 2-year, randomized, double-masked, multicenter studies comparing the efficacy and safety of brolucizumab versus aflibercept in subjects with nAMD. HAWK compares brolucizumab for intravitreal injection at 3 and 6 mg levels with aflibercept 2 mg. HARRIER compares 6 mg of brolucizumab with aflibercept 2 mg.[26] HAWK and HARRIER have just released positive results for the first year of treatment, managing to keep patients at q12 regimen for 57% and 52% of patients, respectively.[27] These results are well above the maximum percentage of patients that can be managed every 12 weeks with aflibercept, which is 35%.[28]

Abicipar pegol (Allergan) is a recombinant protein of the designed ankyrin repeat protein (DARPin) family. DARPins are small, single-domain proteins that can selectively bind to a target protein with high affinity and specificity. These molecules are genetically engineered proteins that mimic antibodies, with greater stability and at least equal affinity with immunoglobulins. Abicipar pegol works in a similar fashion to ranibizumab, pegaptanib, and aflibercept by inhibiting VEGF-A, binding it without receptor interaction. It has shown a number of advantages compared with most anti-VEGF drugs: high potency, very long ocular half-life (about 2 weeks), and very low systemic exposure.

In a phase 1/2 dose escalation study, patients received a single intravitreal injection of abicipar pegol at doses ranging from 0.04 to 3.6 mg with monitoring for 16 weeks for safety, efficacy, pharmacokinetics, and dose response. Thirty-two patients received a single injection of abicipar pegol, in a dose escalating fashion, with a maximum tolerated dose of 1.0 mg due to cases of endophthalmitis in the 2.0 mg cohort. Drug-related adverse events were reported by 13 (41%) of 32 patients; they included ocular inflammation in 11 patients (7 mild, 4 moderate in severity). Final visual acuity was stable or improved compared with baseline for 4 weeks after the injection, showing both retinal thickness and fluorescein angiography leakage decreased. These effects were dose-dependent. Rescue therapy was administered to 20 (91%) of 22 patients who received 0.04–0.4 mg abicipar compared with 4 of 10 (40%) patients who received 1.0 or 2.0 mg. Five out of 6 patients (83%) in the higher dose cohorts who did not require rescue treatment maintained the reductions observed in central retinal thickness through week 16.[29] Based on these results, 2 phase 3 trials (Cedar and Sequoia) were initiated and are being conducted at present, with no results released yet.

ANGIOPOIETIN

Angiopoietin 2 is increased in proangiogenic diseases, including retinal vascular diseases such as pathologic retinal neovascularization. Therefore, selective neutralization of both VEGF and angiopoietin 2 may further normalize the pathologic ocular vasculature in comparison with anti-VEGF monotherapy.[30]

RG7716 (Roche) is a humanized bispecific immunoglobulin G (IgG) monoclonal antibody that simultaneously binds both VEGF and angiopoietin 2 with selective antigen-binding fragments in the same molecule.

In a phase 1 study conducted in the United States and the United Kingdom, 24 patients with previously treated unresponsive neovascular AMD received a single intravitreal injection of 0.5, 1.5, 3, and 6 mg of RG7716. After 28 days, visual acuity gains of 7 letters were reported for the 6 mg group. These results led to a phase 2 study that is being conducted at present.[31]

Nesvacumab (Regeneron) is an antiangiopoietin 2 monoclonal antibody. Unlike RG7716, it only targets angiopoietin 2, so it must be used in combination with aflibercept. In a phase 1 dose escalating study, the nesvacumab-aflibercept combination was demonstrated to be effective and safe. A phase 2 trial in AMD is being conducted at present to further evaluate its efficacy and safety.[32]

VEGF PATHWAY

Upstream

Another way of controlling the VEGF cascade would be to interfere with VEGF production. Small interfering RNA (siRNA) induce short-term silencing of protein coding genes. siRNAs consist of 2 RNA strands that act intracellularly by way of mRNA degradation. If delivered to the correct cells, they would interfere with VEGF by blocking its production.[33]

Bevasiranib (Opko) was the first siRNA for intraocular use. It was tested in combination with ranibizumab (Lucentis) for treatment of neovascular AMD in a phase 3 trial (Cobalt), which was stopped due to lack of efficacy.[34]

Downstream

Squalamine, OHR-102, (Ohr Pharmaceutical) is a small molecule, with antiangiogenic effects based on a novel intracellular mechanism of action. It has the ability to inhibit several growth factors such as VEGF, basic fibroblast growth factor, and platelet-derived growth factor (PDGF).

Activated endothelial cells intake the drug through structures known as caveolae, which are small invaginations in the cellular membrane. Once inside the cell, it binds to calmoduline, preventing downstream signaling of angiogenic factors.[35] Squalamine is delivered to the eye in the form of an eye drop. Clinical evidence has shown these additional growth factors play a major role in angiogenesis and other ocular neovascular disease.

The IMPACT study, a phase 2 evaluation of squalamine eye drops plus ranibizumab versus ranibizumab monotherapy, showed that visual acuity gains were related to the size and type of lesions in this study population. Previously, a positive benefit in terms of visual acuity outcomes was shown in patients whose lesions had a classic component.

Further analysis of lesion type to predict visual acuity gains demonstrated that the smaller the occult CNV size, the greater the effect on visual acuity, with or without classic component. Those patients treated with ranibizumab monotherapy did not show this

lesion type/size to visual acuity benefit.

At present, a phase 3 study is ongoing to further evaluate the efficacy and safety of squalamine eye drops.[36]

PLATELET-DERIVED GROWTH FACTOR

The angiogenesis process can be divided into 5 stages: degradation of basement membranes, migration of endothelial cells, tube formation by endothelial cells, new basement membrane formation, and encirclement by pericytes for stabilization. In-vitro studies have demonstrated that PDGF plays an important role in the angiogenesis process. It has been shown to promote migration and proliferation of endothelial cells along with an increase in the recruitment of pericytes.[37]

Pegpleranib (Fovista; Ophthotech) is a pegylated DNA aptamer that selectively binds to PDGF-BB and PDGF-AB homodimers and heterodimers, interrupting the interaction with their associated tyrosine kinase receptors. These receptors are commonly expressed on pericytes, which stabilize newly formed vessels. By disrupting the effect of PDGF on pericytes, the angiogenic process is negatively affected.

In a phase 2B trial of 449 patients with neovascular AMD, pegpleranib in association with ranibizumab was compared with ranibizumab monotherapy. The study showed that the combination of pegpleranib 1.5 mg and ranibizumab 0.5 mg yielded a 62% relative benefit measured as Early Treatment Diabetic Retinopathy Study visual acuity over ranibizumab monotherapy.[38]

A recent phase 3 study failed to show any benefit for the combination over monotherapy.[39]

Rinucumab (Regeneron) is a monoclonal antibody aimed at blocking PDGF-B. A phase 1 open-label study investigated intravitreal rinucumab combined with aflibercept in 4 cohorts of 3 patients with wet AMD, treated at baseline and at 4 weeks. Visual acuity was stable or increased in most patients, and there were no reports of treatment-related serious adverse events. A phase 2 study (CAPELLA) reported no benefits of the combination therapy over aflibercept monotherapy.[40]

VEGF-C AND -D

Patients receiving anti–VEGF-A treatment for neovascular AMD have been described as having increased vitreous levels of VEGF-C and -D, which may play a role in angiogenesis due to activation via receptors 2 and 3 (VEGFR 2 and VEGFR 3). OPT-302 is a soluble form of VEGFR 3 comprising the extracellular domains 1–3 of human VEGFR 3 and the Fc fragment of human IgG1.

VEGF-C has also been described as producing a potent induction of vascular permeability. Available strategies for treating neovascular AMD patients only manage to block VEGF-A, with no or positive effect on other members of the VEGF family.

In an ideal scenario, blockade of all forms of VEGF should be the best strategy for inhibiting angiogenesis.[41]

A phase 1/2A trial met the primary endpoint and is moving into phase 2.[42]

GENE THERAPY

All treatment strategies addressed so far have the limitation of needing more or less frequent administrations. Intraocular gene therapy has the potential to enable a continuous supply of therapeutic proteins from inside the eye to manage and treat retinal diseases. Leber congenital amaurosis and choroideremia, 2 rare congenital disorders, have been successfully treated with the use of recombinant adeno-associated vectors (rAAVs).

A similar strategy to treat wet AMD has been developed to transduce retinal cells with rAAV encoding sFLT-1, a highly potent naturally occurring VEGF inhibitor, the soluble form of the VEGFR 1 receptor. VEGF-A, VEGF-B, and PlGF have high affinity to VEGFR 1 through its domain 2. Antiangiogenic factors could then be delivered directly at the site where they are needed, as rAAV.sFLT-1 is given via subretinal injection, which places the vector in direct contact with retinal pigment epithelial cells and photoreceptors of the outer retina.[43]

Other approaches involving intravitreal administration of rAAV vectors inducing sFLT-1 production seem to be more successful than subretinal delivery due to a simpler method of administration that does not require a vitrectomy as part of the procedure.[44]

SUSTAINED DELIVERY

Approved anti-VEGF therapies are effective in reducing leakage and halting neovascularization at a cost of frequent visits and injections. Use of anti-VEGF therapy associated with sustained delivery strategy may overcome the burden of visits/injections and possibly permit better long-term results.

The port delivery system, developed by ForSight VISION4 for delivery of ranibizumab, is a refillable, nonbiodegradable drug delivery implant designed to provide sustained release of a drug into the vitreous. The ranibizumab prefilled port is implanted at the level of the pars plana and rests in position covered by the conjunctiva. The placement requires a standard retinal surgical procedure in which no sutures are needed to close the 3.2-mm scleral incision. The total surgical time to place the port is estimated to be 15 minutes or less.

Once the device is implanted, refills can be performed as needed by an office-based procedure, like most intravitreal injections. The device provides continuous release of ranibizumab into the vitreous between refill procedures.

A phase 1 study on 20 treatment-naive patients showed visual gains comparable to those obtained in the ANCHOR and MARINA trials. A phase 2 study is ongoing.

Encapsulated cell technology, another delivery system developed by Neurotech Inc, is a tiny device that is implanted inside the eye. The device contains anti-VEGF drug that leaks out into the eye over time. A recent phase 2 trial was stopped due to lack of effect.[45]

CONCLUSIONS

Anti-VEGF treatment for neovascular AMD has been a turning point in the management of this condition. For the past 10 years, treatment regimens managed to balance injections and visits to lower the burden for patients, caregivers, and the health system. Despite this success, there are several unmet needs that need to be covered by new treatment strategies. Over the next couple of years, hopefully new treatments with better efficacy and longer durability will become available. These treatments still aim at blocking VEGF as their mode of action. Several other targets

are being explored with varied results, which may further expand our armamentarium to successfully halt progression and restore vision in those affected by neovascular AMD.

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