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REVIEW

Bevasiranib for the Treatment of Wet, Age-Related Macular Degeneration

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Abstract: Age- related Macular Degeneration (AMD) is the leading cause of severe visual impairment in people 65 years and older in industrialized nations. Exudative, or "wet", AMD is a late form of AMD (as distinguished from atrophic, so-called dry, AMD) and is responsible for over 60% of all cases of blindness due to AMD. It is widely accepted that vascular endothelial growth factor (VEGF) is a key component in the pathogenesis of choroidal neo-vascularization (CNV), which is a precursor to wet AMD. The current gold-standard for treating wet AMD is the monoclonal antibody fragment ranibizumab (trade name Lucentis), which targets VEGF. Other agents used to treat wet AMD include pegaptanib (Macugen), bevacizumab (Avastin; off-label use), and several other experimental agents. The advent of small interfering RNA (siRNA) has presented a whole new approach to inhibiting VEGF. This article reviews the status of a novel siRNA-based therapeutic, bevasiranib, for the treatment of wet AMD. Bevasiranib is believed to work by down regulating VEGF production in the retina. Studies in human cell-lines and animal models have shown that VEGF siRNAs are effective in inhibiting VEGF production. Although there is a lack of sufficient published data on human studies supporting the use of bevasiranib for wet AMD, available data indicates that due to its unique mechanism of action, bevasiranib might hold some promise as a primary or adjunct treatment for wet AMD.

Keywords: age-related macular degeneration, vascular endothelial growth factor, bevasiranib

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Introduction

Age-related Macular Degeneration (AMD) is the leading cause of severe visual impairment in people 50 years and older in industrialized nations. AMD affects about 14 million people worldwide.[1] AMD ranks third among the global causes of visual impairment and causes blindness in 8.7% of the world's population.[2] The overall prevalence of AMD in the US population 40 years and older is estimated to be 1.47%, which translates into 1.75 million with AMD. Owing to the rapid aging of the US population, this number will increase to almost 3 million by 2020.[3] Wet-type AMD accounts for about 10%–20% of people with AMD; however it is responsible for 90% of AMD-related vision loss.[4]

There are several identifiable risk factors for the development and progression of AMD. These include advanced age, a history of smoking, obesity, family history, diet (high in fat, low in antioxidants and zinc), and Caucasian race. The presence of certain polymorphisms in the gene for complement factor H (Tyr402His variant) and the age-related maculopathy susceptibility 2 (ARMS 2) gene (Ala69Ser variant) have been linked to an increase in susceptibility.[5,6] This review will focus on current advances in the pharmacotherapy of wet AMD, with specific emphasis on the therapeutic potential of the siRNA-based drug bevasiranib in the management of wet AMD.

Pathophysiology of AMD

The macula is situated at the central, posterior area of the retina. It is the region with the densest concentration of photoreceptors and is responsible for central high resolution visual acuity. This region allows the eye to perform specialized functions like deciphering the finer details of objects, reading and facial recognition. The retinal pigment epithelium (RPE) lies posterior to the photoreceptors and comprises part of the blood-ocular barrier. The functions of the RPE include receptor phagocytosis, nutrient transport, and cytokine secretion. A semi-permeable exchange barrier called the Bruch's membrane separates the retinal pigment epithelium from the choroid, which contains the blood supply to the outer layers of the retina.[7,8] As an individual ages, several changes occur within the eye. Significant age-related changes include the focal deposition of acellular, polymorphous debris between the retinal pigment epithelium and Bruch's membrane. These deposits, called drusen, are pale, yellowish lesions that can be seen during fundoscopic examination on the macular and the peripheral retina.[7,8]

The presence of drusen is usually the first clinical finding of AMD; however, a few drusen in people over 50 years of age may be considered part of the normal aging process. On the other hand, a large deposit of drusen can lead to RPE damage, which can subsequently induce a chronic aberrant inflammatory response characterized by the atrophy of large areas (geographic atrophy) of the retina and/or the expression of cytokines such as vascular endothelial growth factor (VEGF). AMD can be classified into two broad groups; "dry" or atrophic (non-neovascular) and "wet" or exudative (neovascular) AMD. While dry AMD is characterized by the presence of drusen and geographic atrophy, wet AMD is characterized by choroidal neo-vascularization (CNV), exudation, and other consequences of neo-vascularization (detailed below).[7,8] The exact mechanism by which drusen are involved in the pathogenesis of AMD remains unclear; however, some investigators believe that complement proteins such as C3a and C5a within the drusen may play a role in enhancing the expression of VEGF, as suggested by both *in vivo* and *in vitro* studies.[9] The over-expression of VEGF leads to CNV, increased vascular permeability and vascular fragility. This neo-vascularization could extend anteriorly through breaks in the Bruch's membrane, leading to subretinal hemorrhage, fluid exudation, lipid deposition, fibrotic scarring, and detachment of the RPE from the choroid.[7,8]

VEGF

A significant and well-studied component of wet AMD pathogenesis is VEGF-mediated CNV. VEGF (also known as VEGF-A) is a key member of a family of dimeric glycoproteins that belong to the platelet derived growth factor (PDGF) family of growth factors. This family includes, VEGF-A, VEGF-B, VEGF-C, VEGF-D, placental growth factor (PGF)-1 and PGF-2. There are several isoforms of VEGF-A, including VEGF-A121, VEGF-A145, VEGF-A148, VEGF-A183, VEGF-A189 and VEGF-A206; the best characterized pro-angiogenic isoform of VEGF is VEGF-A165.[10,11]

VEGF gene expression is regulated by physiological factors such as hypoxia, growth factors and nitric oxide.

In animal studies, over expression of VEGF in the RPE was sufficient to cause CNV in the rat retina and the subsequent death of photoreceptor cells.[12]

Most of the mechanisms that have been exploited in the management of AMD are aimed at inhibiting the angiogenic function of VEGF. Monoclonal antibody-based approaches are designed to directly target VEGF or its receptors. Another class of drug, exemplified by VEGF Trap, is so-called decoy-receptor, a protein that mimics the VEGF receptor, binding to and inactivating VEGF. Yet another approach is to inhibit the downstream functions of VEGF function by inactivating VEGF receptor tyrosine kinase activity. More recently, a unique class of drugs has been developed that targets the mRNA encoding VEGF. Such small interfering RNA (siRNA)-based drugs have been developed that silence the mRNAs encoding VEGF or the VEGF receptor.

Current Therapy for Wet AMD

There are several drug options for treating wet AMD, each associated with different mechanisms of actions, side effects and frequency of administration. The preference among these different drugs will depend on efficacy, safety, and patient comfort. Since the key drugs are all administered intra-vitreally, frequency of administration is also very important (Table 1). The anti-VEGF approach has been very successful, and clinical trial results clearly support the use of this broad class of therapeutics.

Pegaptanib

The first intra-vitreal agent approved by the United States Food and Drug Administration (FDA) for the treatment of wet AMD was pegaptanib (Macugen®), which was developed by OSI Pharmaceuticals in 2004. It is an mRNA aptamer and a VEGF antagonist. In a randomized, double-blind, multicenter, dose-ranging, controlled clinical trials in 1186 patients, intravitreal injections of pegaptanib at three different doses into one eye per patient or sham injections were administered once every 6 weeks over a period of 48 weeks.[13] The primary end point was proportion of patients who had lost fewer than 15 letters of visual acuity at 54 weeks. In the combined analysis of the primary end point efficacy was demonstrated, without a dose-response relationship, for all three doses of pegaptanib ($P < 0.001$ for the comparison of 0.3 mg

Table 1. Summary of drugs that are currently used for wet-AMD or are in advanced clinical trials.

Drug	Classification	Mechanism of action	Route of administration	Frequency of administration	Serious adverse effects	Clinical trial status
Ranibizumab (Lucentis)	Monoclonal antibody	Inhibits all VEGF-A isoforms	Intravitreal	Every 4 weeks	Thromboembolism, retinal detachment, iridocyclitis	Phase IV
Pegaptanib (Macugen)	RNA aptamer	Inhibits VEGF-A165 isoforms	Intravitreal	Every 6 weeks	Reduced visual acuity, endophthalmitis, retinal detachment	Phase IV
Bevacizumab (Avastin)	Monoclonal antibody	Inhibits all VEGF-A isoforms	Intravitreal	†Every 4 weeks	Thromboembolism, retinal detachment	Phase III
Bevasiranib (formerly Cand5)	siRNA	‡RNA interference inhibits the formation of VEGF-A	Intravitreal	¶Every 12 weeks	No data available	Phase III
VEGF Trap-Eye	Recombinant protein	Acts as VEGF receptor decoy targeting VEGF-A, VEGF-B, and PIGF	Intravitreal	§Every 4 or 12 weeks	No data available	Phase III

Notes: †Available data suggests that bevacizumab (off-label use) might be effective with every 8–12 week administration;[40] ‡Also believed to act via TLR3;[20,21] ¶Dosing frequency tested in clinical trials (not yet FDA approved); §Dosing options are still being tested in clinical trials (not yet FDA approved).

with sham injection; $P < 0.001$ for the comparison of 1.0 mg with sham injection; and $P = 0.03$ for the comparison of 3.0 mg with sham injection) concluding that all three doses have similar efficacy when compared to sham injection. Serious adverse effects included endophthalmitis (1.3%), traumatic injury to the lens (0.7%), and retinal detachment (0.6%). These events were associated with a severe loss of visual acuity in 0.1% of patients.[13] Recent clinical data suggest that pegaptanib might be better used as a maintenance drug.[14] Since pegaptanib is a selective VEGF inhibitor that blocks only the VEGF-A165 isoform, it has been suggested that it might be efficacious in an induction-maintenance treatment strategy that uses a non-selective followed by a selective VEGF antagonist, particularly in patients with other co-morbidities who require long term anti-AMD therapy.[14]

Ranibizumab and bevacizumab

The most commonly used drugs for treating wet-AMD are ranibizumab (Lucentis®) and bevacizumab (Avastin®), both of which were developed by Genentech. Ranibizumab, considered the "gold-standard" by most, is a fragment of a humanized monoclonal antibody that binds to and inhibits all isoforms of VEGF-A. It is administered monthly by intra-vitreal injection.[15] Severe adverse events are rare but include endophthalmitis and uveitis.[16] The MARINA study was a randomized, double-masked clinical trial involving 716 patients with AMD who received monthly intra-vitreal ranibizumab (0.3 or 0.5 mg) or sham injections. The effects of ranibizumab on patient-reported visual function were evaluated using the National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25). The results showed that ranibizumab-treated patients had a higher overall improvement in vision as compared to the control sham-injected group (95% CI, –4.6 to –1.1; $P < 0.001$).[17]

Bevacizumab is also a humanized monoclonal antibody specific for VEGF. It is approved by the US FDA for cancer treatment, especially colorectal cancer when given intravenously, but is increasingly being used off-label as intra-vitreal injection for the treatment of wet-AMD.[18] Available data show that bevacizumab has a similar safety and efficacy profile as ranibizumab when used for wet AMD.[19–22] Interestingly, bevacizumab might have an advantage over ranibizumab in terms of frequency of administration. In a recent study assessing intra-vitreal treatment of AMD, bevacizumab administered at three-month intervals maintained its efficacy in most patients as compared to baseline ocular function ($P = 0.003$).[23]

Intra-vitreal injection poses a significant limitation for most current drug therapies. The complications of repeated intravitreal injection might include endophthalmitis, retinal tears, intravitreal bleeding, and lens injury. In a multicenter retrospective study of 920 patients with wet AMD receiving intra-vitreal bevacizumab over a two year period, 1.6% developed tears in the RPE.[24] Endophthalmitis is inflammation of the internal coating of the eye usually as a result of infection or trauma. It can lead to blindness if not treated properly and in a timely manner.[25] As reported in a case study of an 83 year old patient with macular edema from branch retinal vein occlusion (BRVO) in the right eye and neovascular macular degeneration in the left eye, bevacizumab administered into the left eye temporarily improved the macular edema in the right eye, and intra-vitreal injection of ranibizumab into the left eye resulted in a significant reduction of macular edema in the right eye.[26] While it is unclear what these results mean in terms of efficacy of the two drugs, leakage into the systemic circulation appears possible, which increases concerns about systemic side effects. Both drugs have similar, rare but serious systemic side effects, including increased risk of thromboembolic events (Table 1). Given that all of the currently approved anti-VEGF agents require intra-occular injections every 4–6 weeks, the risk of developing the above-mentioned rare but serious side effects increases over time and with repeated administrations. We shift our focus now to a new, potentially longer acting agent, bevasiranib, which is showing promise as an adjunct treatment, thereby perhaps reducing the burden of frequent intra-vitreal injections.

Bevasiranib

The 2006 Nobel Prize-winning work of Andrew Fire and Craig C. Mello on RNA interference (RNAi)[27] opened up a new era in drug research and development. Interest in the applications of RNAi technology, especially in the development of new therapeutics for various diseases, including wet AMD, has been on the rise, and there are currently at least eight drugs in

various stages of clinical trials that use this mechanism to treat different diseases conditions.[28]

Bevasiranib (formerly known as Cand5): initially developed by OPKO Ophthalmologics, is a siRNA-based anti-angiogenic agent proposed for the treatment of wet AMD. Administered as bevasiranib sodium, the chemical structure is a complex of two 21-nucleotide RNA eicosasodium molecules.[29] In various cell systems, 21-nucleotide RNA duplexes have been shown to suppress the expression of endogenous and heterologous proteins in a gene-specific manner.[30] Bevasiranib follows the traditional approach of targeting VEGF, and thus preventing and/or reversing the CNV associated with wet AMD.

Mechanism of action

Upon introduction into the cell, a siRNA binds to and activates the RNA-induced silencing complex (RISC). The RISC in turn targets and degrades mRNA molecules that are complementary to the introduced siRNA. A single activated RISC complex can bind to and destroy hundreds of mRNAs, thus preventing translation and protein synthesis.[31] As such, RNAi represents a very efficient mechanism for preventing the expression and synthesis of unwanted or harmful proteins. Because one RISC molecule can suppress the expression of several hundred protein molecules, RNAi is an ideal therapeutic strategy for the eye, which, because of its limited volume, requires potent molecules for effective local administration.[32] Furthermore, mRNA stabilization is believed to be the primary mechanism of VEGF up-regulation, as opposed to transcription.[33] Thus, post-transcriptional RNAi-induced gene silencing is a particularly effective approach to blocking the effects of VEGF, but preventing synthesis in the first place. Because bevasiranib down-regulates the VEGF-A mRNA, it represents a departure from the approaches of current anti-VEGF agents, which simply target VEGF protein by either binding directly to VEGF or the VEGF receptor, or by inhibiting VEGF downstream events. By silencing the synthesis of VEGF protein, bevasiranib can prevent the ocular changes associated with wet AMD.

Results of recent studies have suggested that VEGF-targeted siRNAs might act via an alternative mechanism, through toll like receptor 3 (TLR3), in preventing CNV.[34,35] In experiments comparing TLR3 wild-type ($Tlr3^{+/+}$) and TLR3 knockout ($Tlr3^{-/-}$) mice, intra-vitreal injection of an anti-VEGF siRNA suppressed CNV in $Tlr3^{+/+}$ but not $Tlr3^{-/-}$ mice suggesting involvement of TLR3. Furthermore, to separate the RNAi activity from the TLR3 activity of the siRNA, the siRNA nucleotides were modified with 5-methoxy (CH_3O), which prevents their incorporation into the RISC. This modified siRNA suppressed CNV in wild-type mice as effectively as the unmodified VEGF siRNA, and was ineffective in $Tlr3^{-/-}$ mice.[34] These results suggest that anti-VEGF siRNA can suppress CNV through an alternate mechanism involving TLR3. Importantly, these results indicate that the anti-CNV action of bevasiranib may be due at least in part to TLR3-mediated activity, and not exclusively to VEGF gene silencing and VEGF production.

Pharmacokinetics

Bevasiranib sodium was developed for intra-vitreal administration, and like other intra-vitreal anti-angiogenic agents, requires knowledge of specialized injection techniques.

Following intra-vitreal injection, bevasiranib is well distributed within the eye and localizes to the retina.[36] In pre-clinical biodistribution experiments, single intra-vitreal injection of 0.5 mg or 2 mg of radio-labeled bevasiranib into the rabbit resulted in distribution of bevasiranib throughout the eye (aqueous fluid, iris, vitrous fluid, retina and sclera).[36] The concentration of intact (non-degraded) bevasiranib in eight tissues was also measured (aqueous fluid, vitreous fluid, lens, iris, ciliary body, RPE, choroid and retina), because in order to be effective, the drug must survive degradation by tissue nucleases. The goal in drug administration in wet AMD is for the drug to reach the retinal pigment epithelium-Bruch's (RPE-B) membrane-choroidal complex. Relatively high amounts of bevasiranib were measured within the RPE-B, which indicates that the drug is well distributed within the eye and reaches its target tissues.[36] There is currently no publically available data on the metabolism or elimination of bevasiranib.

Pre-clinical studies

In transfection studies using human cell lines, anti-VEGF siRNA abolishes the hypoxia-induced up-regulation of VEGF.[37] Human 293 embryonic kidney

cells and ovarian carcinoma (HeLa) cells transfected with an anti-VEGF siRNA (hVEGF5 siRNA) were exposed to desferrioxamine for 24 hrs to induce hypoxia. Hypoxia activates the HIF-1 hypoxic signaling pathway, which upregulates VEGF expression in the cells. Treatment with a non-specific siRNA had minimal effects on VEGF levels in hypoxic 293 and HeLa cells, whereas VEGF expression was significantly decreased by treatment with hVEGF5 siRNA as compared to control treated cells or non-hypoxic cells In a laser photocoagulation-induced model of CNV in mice, mice were administered bilaterally sub-retinal injections of an hVEGF-containing recombinant adenovirus in the presence or absence of hVEGF siRNA. A control non-specific siRNA was administered into the contra-lateral eye. Co-injection of hVEGF5 siRNA resulted in a significant reduction in the levels of hVEGF as compared to the control siRNA ($P < 0.0013$). These findings demonstrated that RNAi is an effective approach to the silencing of VEGF mRNA *in vitro* and in animals.[37] In conclusion, siRNA targeting *mVegf* is capable of inhibiting CNV in the laser photocoagulation model.

In a separate study, in both *in vitro* and *in vivo* models, treatment with a VEGF siRNA suppressed the expression of endogenous VEGF.[38] In human umbilical vein endothelial cells (HUVECs), recombinant vector-driven expression of an siRNA that targeted $VEGF_{165}$ (*pSilencer.siVEGF*) suppressed the expression of $VEGF_{165}$, the most active of the VEGF isoforms involved in pathologies of the eye. The same siRNA system substantial inhibited $VEGF_{165}$ expression in mice as compared to treatment with no siRNA ($P < 0.05$).[38]

The efficacy and safety of intra-vitreal injection of bevasiranib in reducing the growth and leakage of blood vessels have been carried out in a non-human primate model of CNV.[32,39] Cynomologous monkeys with laser-induced CNV were treated with three doses of bevasiranib (70 µg, 150 µg, or 350 µg of anti-VEGF siRNA (bevasiranib). Eyes were monitored weekly by ophthalmic examination, color photography and fluorescein angiography for 36 days after laser injury. Electroretinograms were measured at baseline and at 5 weeks after laser treatment. CNV on fluorescein angiograms was measured to determine area and graded for clinically significant leakage in a standardized, randomized, and double-masked fashion on days 15, 22, 29, and 36. Bevasiranib significantly inhibited the growth of the neovascular area as compared to control animals ($P < 0.0001$ for all three doses). The overall reduction in CNV area in the bevasiranib groups was greater than 50% of the control group. Vascular leakage as determined by fluorescein angiograms showed that bevasiranib reduced vascular exudation significantly in a dose dependent manner ($P = 0.0007$). These results were confirmed by histological analysis.[32,39]

Clinical trials

Preliminary results of Phase 1 and 2 clinical trials of bevasiranib have shown promising results for the treatment of wet AMD and diabetic macular edema,[40] but there is no data in the literature presenting the results in detail. The remainder of this review will focus on available data from clinical trials to determine what role, if any, bevasiranib might play in the treatment of wet AMD.

In a non-randomized, open label, dose comparison, phase I study to establish the tolerability and preliminary efficacy of bevasiranib administered by single intra-vitreal injection, 15 patients with wet AMD were assigned into five dosing groups of 0.1 mg, 0.33 mg, 1 mg, 1.5 mg, and 3 mg bevasiranib. Eligibility included sub-foveal predominantly classic, minimally classic and purely occult lesions secondary to AMD; total lesion size (including blood, atrophy/scar and neovascularization) of <12 total disc areas, of which at least 50% comprised active CNV; visual acuity of 20/50 to 20/320 in the study eye; better visual acuity in the contra-lateral eye; and sub-retinal hemorrhage ≤50% of the total lesion size. Patients were excluded if they had concomitant eye disease, including glaucoma, uveitis, diabetic retinopathy, presence of pigment epithelial tears or rips, acute ocular or peri-ocular infection in the study eye. Also excluded were patients that had undergone >3 prior photodynamic therapy (PDT) sessions with visudyne or received PDT in the study eye within eight weeks prior to the baseline angiography/photography. Results of this study have not been published, which makes it difficult to have all needed details to judge the outcome.[41]

A phase II randomized, double blind, dose comparison study evaluating the safety and preliminary efficacy of bevasiranib in the treatment of wet AMD

is currently underway. A total of 120 patients will be assigned to three dosing groups (0.2 mg, 1.5 mg, and 3 mg intra-vitreally). Patients included in this study must have sub-foveal classic, predominantly classic, or minimally classic lesions, secondary to AMD. They must have an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart best corrected visual acuity of 64 to 24 letters (20/50 to 20/320 Snellen Equivalent) in the study eye, and be over 50 years of age. Exclusion criteria include prior treatment with any investigational new drug or device for wet AMD in the study eye within 24 weeks of the screening visit; advanced glaucoma (greater than 0.8 cup:disk) or intraocular pressure above 22 mmHg in the study eye; any retinal vasculopathy, including diabetic retinopathy; and retinal vein occlusions in the study eye. Patients whose CNV lesion in the study eye consisted of greater than 25% scar tissue and/or atrophy or exhibited greater than 25% sub-foveal scarring, atrophy or hemorrhage; who had undergone any extrafoveal/ juxta-foveal laser treatment in the study eye within two weeks of screening; or who had received treatment with an investigational drug within 4 weeks prior to the screening visit were also excluded. The primary outcomes of the study are change from baseline in macular edema as measured by optical coherence tomography; secondary outcome is mean best corrected visual acuity (BCVA) line/letters change from baseline at the 12-week evaluation period. The detailed results of this study have not been made public.[42]

A recent Phase III trial, a randomized, double blinded, controlled trial examining the safety and efficacy of the combination of bevasiranib and Lucentis® (the COBALT Study) was terminated on the recommendation of the study's Independent Data Monitoring Committee (IDMC), which determined that it was unlikely to attain its primary objective. The COBALT study was designed to compare the safety and effectiveness of bevasiranib administered once every 8 weeks or once every 12 weeks after an initial pretreatment with 3 injections of Lucentis® and Lucentis alone administered every 4 weeks.[43] A new phase III study evaluating the combination of bevasiranib and Lucentis in Wet AMD (the CARBON study) is currently underway. The purpose of this study is to compare the safety and effectiveness of three doses of intra-vitreal bevasiranib sodium as maintenance therapy for AMD following initiation of anti-VEGF therapy with three doses of Lucentis.[44]

Preliminary clinical results indicate that the effects of bevasiranib do not appear until six week after the commencement of treatment, which suggests that combination therapy when using bevasiranib as an adjunct might be justified.[40] The notion that the effect of bevasiranib is appearing late might be linked to its mechanism of action since bevasiranib inhibits the synthesis of new VEGF, and does not eliminate existing VEGF, a direct anti-VEGF agent may be required to neutralize VEGF already present in the eye before the effects of inhibiting new VEGF synthesis are realized. Preliminary results of the CARBON and COBALT studies suggested that over 30% of patients on combination Lucentis-bevasiranib achieve at least three more lines of visual acuity than those on Lucentis alone.[40] The safety and efficacy of this combination awaits the full results of the ongoing clinical trials.

Conclusion

Although the safety profiles and efficacy results of clinical trials are promising, the lack of available data from randomized placebo controlled or comparative studies makes it difficult to objectively evaluate the role of bevasiranib in wet AMD therapy. It is clear from experimental and pre-clinical studies that anti-VEGF siRNA (either bevasiranib or similar formulations) technology is capable of down regulating VEGF production, a key goal of anti-VEGF therapy. Testing in animal models has shown that intra-vitreal injection of bevasiranib results in good biodistribution, especially within the retina and the RPE, which indicates that the drug gets into target tissues intact and largely escapes degradation by intraocular nucleases, a key goal in intraocular drug delivery. Targeting of VEGF with siRNA has also been shown in animal models to counter VEGF production and reverse CNV, by both chemical and histological analysis.

Delivery of siRNA molecules into humans is a major challenge. In humans, bevasiranib is delivered as a naked siRNA molecule, unlike in animal models in which the agent is delivered using a transfection agent. Some researchers have suggested that naked RNA is not taken up into cells, and that the positive results seen with bevasiranib are due to an innate immune reaction mediated by TLR3.[45] While this possibility certainly warrants further investigation,

iRNA technology, which inhibits the synthesis of new VEGF, appears to be a rational approach, particularly as maintenance therapy, since it may have a slower onset and longer duration of action than other anti-VEGF agents. The results of the CARBON trials, when available, will shed more light on this possibility.

With few exceptions, wet AMD therapy involves intra-vitreal administration of drug therapy. This route of administration is necessary in order to localize the drug to the eye, and prevent or at least limit potential systemic adverse effects. This brings up the major concern of patient discomfort and the obvious risks that frequent injections into the eye pose. Ongoing research is targeted at developing either longer acting agents or more conducive means of administering currently available ones. In this respect bevasiranib might be a good option, as studies to date indicate that eight or twelve-week administrations are equally effective. The development of a topical form of bevasiranib would significantly enhance its clinical appeal.

In summary, bevasiranib exploits an interesting technology and may be a useful addition to the currently available drugs used to treat wet AMD. It is worth noting that siRNA technology is currently being tested in various other diseases such as solid-tumors, advanced immunodeficiency syndrome, hepatitis B, pachyonychia congenital, and respiratory syncytial virus (RSV) infection. Also, bevasiranib is not the only siRNA agent that currently being tested for wet AMD. Another drug, AGN211745 (formerly SIRNA-027), which targets the VEGF receptor (VEGFR-1) is also currently in clinical trials after showing favorable results in animal testing.[46] Thus, the future appears promising for siRNA and other RNAi based pharmaceuticals.

Abbreviations

AMD, wet age-related macular degeneration; VEGF, vascular endothelial growth factor; CNV, choroidal neo-vascularization; siRNA, small interfering RNA; RPE, retinal pigment epithelium.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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