

What is New in the Management of Age-Related Macular Degeneration?

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Abstract: Age-related macular degeneration (AMD) is a multifactorial, degenerative retinal disease that is the leading cause of irreversible vision loss in individuals over the age of 50 years. Dry (nonneovascular) AMD, characterized by drusen, is typically gradual, insidious and may not progress to total vision loss. Wet (neovascular) AMD, characterized by choroidal neovascularization (CNV) results in severe visual loss in advanced stages. Multiple studies have shown that manipulation of nutritional factors such as antioxidant vitamins, zinc, lutein, omega-3 long-chain polyunsaturated fatty acid, and taurine play a significant role in slowing the effects of dry AMD. Although laser photocoagulation of drusen leads to their disappearance, it does not reduce the risk of developing CNV, geographic atrophy or visual acuity loss. Rheopheresis can improve the natural course of AMD and has emerged as a safe and effective modality for high-risk patients with dry AMD and no therapeutic alternative. Thermal laser photocoagulation, photodynamic therapy with verteporfin, and the anti-vascular endothelial growth factor (VEGF) drugs such as pegaptanib (Macugen; OSI-Eyeteck, Inc., Melville, NY), ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), and bevacizumab (Avastin; Genentech) are the several proven treatment options available for neovascular AMD. The advent of antiangiogenic therapies has revolutionized the management of neovascular AMD. VEGF Trap (Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA), Vatalanib (receptor tyrosine kinase-inhibitor) and Squalamine lactate (Evizon[®], Genaera Corporation, Plymouth Meeting, PA) are other anti-VEGF drugs undergoing trials. Combination therapy including anti-VEGF and anti-platelet-derived growth factor has been shown to produce inhibition and regression of CNV compared with anti-VEGF treatment alone. Triple therapy combining bevacizumab, Verteporfin-Photodynamic Therapy, and dexamethasone attacks CNV through three different mechanisms. Besides color fundus photos, fluorescein angiography and fundus autofluorescence, Optical Coherence Tomography (OCT) has emerged as an outstanding tool for assessing effects of drugs on CNV because it provides an objective measure of the amount of fluid within or under the retina. As more is understood about the pathogenesis of AMD, newer targets include subretinal fibrosis, atrophy, non-VEGF angiogenesis, scar formation, and inflammation which are the other important contributors to vision loss.

Age-related macular degeneration (AMD) is a multifactorial disease with characteristics that include drusen, hyperpigmentation and/or hypopigmentation of the retinal pigment epithelium (RPE), geographic atrophy (GA) and, in a subset of patients, late-stage choroidal neovascularization (CNV). It is the leading cause of blindness in the developed world among aging adults¹. It damages the integrity of the Bruch's membrane and other tissues underlying the macula. Drusen, acellular deposits of lipids, proteins, and inflammatory mediators, are present in nonneovascular AMD, which is often called dry or atrophic AMD. Neovascular AMD also called wet or exudative AMD is characterized by a CNV emanating from the choroid through Bruch's membrane and proliferating below or above the RPE, below the retina in the macular region, resulting in severe visual loss in advanced stages².

Dry AMD is typically gradual and insidious and may not progress to total vision loss. It is the more common form, but wet AMD, which accounts for only about 15% of cases of all AMD, is responsible for nearly 80% of AMD-related cases of severe vision loss³.

To date, there have been considerable advances in the management of wet AMD, but there is still no established treatment for the most prevalent dry form of AMD. Left untreated, patients with dry AMD are at risk for substantial vision loss and progression to wet AMD. The National Eye Institute (NEI), the Macular Degeneration Foundation, Inc., the Macular Degeneration Partnership and Macular Degeneration Support provide the following recommendations for slowing down, or preventing the progression of, **both dry and wet AMD**.

- **Diet and weight control:** Studies suggest that eating antioxidant-rich foods such as fresh fruits, dark green leafy vegetables (a good source of lutein) and at least one serving of fish per week may delay the onset or reduce the severity of dry AMD; in addition, obesity may increase the risk for progression to advanced AMD.
- **Nutritional supplements:** Supplements containing high doses of antioxidant vitamins, copper, and zinc may reduce the risk of

developing advanced AMD by approximately 30%.

- **Blue Light:** Avoid ultraviolet and blue light (particular light waves that make the sky, or any object, appear blue) as much as possible and wear sunglasses that block blue light.
- **Control blood pressure:** Individuals with hypertension are more likely to have wet AMD than persons without hypertension.

DRY AMD

Oxidative stress, formation of drusen, accumulation of lipofuscin, local inflammation and reactive gliosis are implicated in pathogenesis of atrophic AMD. These patients typically develop gradual, insidious visual loss with central or pericentral visual scotomas, over months to years. There is no effective interventional therapy for maintaining or improving vision associated with dry AMD. The current recommendation is an oral supplement containing high doses of antioxidants and zinc, which was tested by the NEI in a large, multi-center trial⁴.

ANTIOXIDANT THERAPY

Multiple studies have suggested that manipulation of nutritional factors can play a significant role in slowing the onset or limiting the effects of AMD.

The Age-Related Eye Disease Study (AREDS), a randomized controlled clinical trial of high-dose antioxidant vitamins (vitamins C, E, and β -carotene) and minerals (zinc and copper), demonstrated that the combination of antioxidant vitamins and zinc treatment reduce the risk of progression to advanced AMD by 25%⁵.

Another multicentric trial demonstrated that dietary omega-3 long-chain polyunsaturated fatty acid intake is associated with a decreased risk of progression from bilateral drusen to central GA⁶.

In the Nutritional AMD Treatment phase I (NAT-1) trial, feasibility of oral supplementation with fish oil (docosahexaenoic acid [DHA]; eicosapentaenoic acid [EPA]) in AMD⁷. Significant enrichments in DHA and EPA levels were observed in the blood of patients receiving these supplements versus controls. There were no side-effects, no

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dropouts and no conversion to CNV in the observed period of study. This study encourages further evaluation of DHA supplementation in AMD.

Based on certain similarities (associated with amyloid deposits) between drusen formation in AMD and Alzheimer's disease (AD), the effect of Copaxone on drusen in dry AMD was tested to assess if it is similar to that on deposits of other age-related chronic neurodegenerative diseases such as AD. Preliminary reports on weekly vaccination with Copaxone (glatiramer acetate) have shown that Copaxone reduces drusen area⁸.

The Carotenoids and co-antioxidants in Age-Related Maculopathy (CARMA) Study, a randomized controlled clinical trial, was developed to test the hypothesis that a combination of antioxidant vitamins, including lutein (L) and zeaxanthin (Z), would be beneficial in maintaining visual function and reducing the risk of progression to a more severe morphological state⁹. The rationale for adding L and Z to the antioxidants (already proven to have a beneficial effect in the AREDS Study) are two-fold: first, L and Z exhibit the ideal anatomic, biochemical, and optical properties to limit oxidative damage at the macula; second, carotenoids act synergistically with other antioxidants to exert antioxidant effect. The CARMA Study is an important interventional study of antioxidant supplementation in AMD patients. Similar to AREDS II, the CARMA Study is a randomized, double masked, and placebo controlled clinical trial of L and Z along with co-antioxidants in AMD participants with a reasonably good sample size.

In 2004, the Lutein Antioxidant Supplementation Trial (LAST) demonstrated that nutritional supplementation with lutein or lutein together with antioxidants, vitamins, and minerals improved visual function and symptoms in patients with atrophic AMD¹⁰.

The influence of short-term carotenoid and antioxidant supplementation on retinal function in dry AMD was assessed in the Carotenoids and antioxidants in age-related maculopathy italian study (CARMIS) by multifocal electroretinograms at baseline and, after 6 and 12 months of therapy¹¹. It was found that a selective dysfunction in the central retina (0 degrees -5 degrees) can be improved by the supplementation with carotenoids and antioxidants. No functional changes were present in the more peripheral (5 degrees -20 degrees) retinal areas.

BEYOND AREDS: THE TOZAL STUDY – A PARADIGM SHIFT IN THE TREATMENT OF AMD

The TOZAL Study incorporated *taurine, omega-3 fatty acids, zinc, antioxidants and lutein*. With the exception of taurine, this formulation is very similar to the AREDS II formulation that is in the first year of a six-year trial. This study sought to identify the potential benefits of a novel supplement designed to limit the risk of AMD and progressive vision loss while also reducing or eliminating the risk of adverse events¹². The results of the TOZAL study agree with the LAST and CARMIS studies and are predictive for positive visual acuity outcomes in the AREDS II trial.

LASER TREATMENT OF DRUSENS

The most common complications in AMD are CNV and loss of photoreceptors causing GA. It has been observed clinically that laser photocoagulation of drusen leads to their disappearance, and was thus proposed as a way to prevent the development of CNV and GA. A review of nine studies using this modality of treatment confirmed the clinical observation that laser photocoagulation of drusen leads to their disappearance¹³. However, there was no evidence that this subsequently reduced the risk of developing CNV, GA or visual acuity loss.

In a study aimed to investigate whether mild laser treatment of soft

drusen maculopathy might reduce the incidence of CNV and/or significantly reduce loss of visual acuity compared with outcomes in a control group, it was concluded that mild prophylactic laser treatment of soft drusen maculopathy was neither beneficial nor harmful and could not be recommended¹⁴.

THE DRY AMD TREATMENT WITH RHEOPHERESIS TRIAL (ART)

Several clinical trials in Germany and the US have evaluated the efficacy of Rheopheresis in AMD¹⁵⁻¹⁸. Rheopheresis is a specific method of therapeutic apheresis, using the methodology of double filtration plasmapheresis, which can be successfully used to improve microcirculatory impairment. Repetitive pulses of plasma protein elimination with a decrease of blood and plasma viscosity by Rheopheresis result in sustained improvements in the microcirculation. This seems to restore and activate or stabilize the functional reserve of the retina at microcirculatory levels.

In the first randomized, controlled clinical investigation, patients in the Rheopheresis group had on average a significant benefit in their visual acuity compared with the no-treatment control group after 3 months¹⁵. The subgroup of eyes with dry AMD and soft drusen showed best results. A pilot trial in the US confirmed a favourable effect from Rheopheresis for patients with dry AMD and soft drusen¹⁶. Rheopheresis is emerging as a therapeutic option for patients with dry AMD with psychological strain, soft drusen, or/and initial atrophy, and pigmentary abnormalities, and visual acuity of 0.1-0.63 in the better eye, without exudation or hemorrhage. Rheopheresis as treatment for dry AMD requires interdisciplinary cooperation between the ophthalmologist for indication and patient evaluation and the nephrologist for performing the treatment.

ANECORTAVE ACETATE

Anecortave acetate (Retaane[®], Alcon Research, Ltd., Fort Worth, TX, USA), is an angiostatic steroid that does not exhibit glucocorticoid receptor-mediated activity. It is delivered as a posterior juxtasclear depot of 15 g every 6 months. Because of its favourable dosing schedule and delivery and low risk profile, anecortave acetate is being studied in the Anecortave Acetate Risk Reduction Trial (AART) for the prevention of CNV in patients with eyes at high risk of converting from non-neovascular to neovascular AMD. This study targets patients with bilateral large size drusen and pigment changes who have a particularly high 5-year risk of progression to advanced AMD¹⁹.

WET-AMD: CURRENT TREATMENT OPTIONS

During the past four decades there have been some highly encouraging improvements in the management of CNV secondary to AMD. Several proven treatment options available for neovascular form of AMD are thermal laser photocoagulation, photodynamic therapy with verteporfin, drugs targeted at VEGF such as pegaptanib (Macugen; OSI-Eyetech, Inc., Melville, NY), ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), and the off-label use of agents such as intravitreal bevacizumab (Avastin; Genentech)²⁰⁻²⁴. In addition, many clinicians and investigators have reported promising results with the agents such as intravitreal triamcinolone acetonide, or the use of various agents in combination²⁵. The efficacy of these treatments is primarily determined by assessing visual acuity outcomes; however, fluorescein angiography (FA) and optical coherence tomography (OCT) measurements are often used as secondary outcome parameters²⁶.

LASER PHOTOCOAGULATION

Panretinal photocoagulation was the earliest treatment for Wet AMD.

Severe visual loss was reported to be less likely in laser-treated patients having risk of developing CNV than no treatment at all^{27,28}. The Macular Photocoagulation Study Group demonstrated a decreased incidence of visual loss in patients undergoing argon laser photocoagulation²⁷. But persistent and recurrent neovascularization associated with severe visual loss were the drawbacks observed with laser treatment²⁹. Other limitations include destruction of overlying retina causing permanent visual loss, making it unsuitable for subfoveal CNV as well as for occult CNV.

VERTEPORFIN PHOTODYNAMIC THERAPY

With PDT, a light-sensitive dye (Verteporfin) is injected intravenously, gets accumulated in the choroidal vessels that are growing abnormally. A blue laser beam is then shone onto the macula to activate the dye. It releases reactive oxygen species, destroying the leaking blood vessels without damaging the healthy tissue around them. More than one sitting is usually required. Blood vessels that have been eradicated in this way do not grow back. However, continued expression of VEGF leads to formation of other new vessels. The first trial to report the benefits of V-PDT was the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) study³⁰. Several studies have shown PDT to be safe and effective for treating classic or predominantly classic CNV³⁰⁻³⁴.

An adjustment of the PDT spot size to include the detection by ICG feeding complex has been shown to be an additional option in the treatment of the subfoveal CNV in cases where anti-VEGF treatment is not available³⁵.

INTRAVITREAL CORTICOSTEROIDS

Inflammation is believed to be a significant factor in the pathogenesis of AMD. Corticosteroids act by reducing inflammation, blocking the up-regulation of VEGF, reducing vascular leakage as they close up the gaps between endothelial cells in the capillary walls. They also limit fibrosis, reducing the scarring in the retina. Intravitreal triamcinolone acetonide has been shown to stabilize the progress of AMD clinically, and to improve visual acuity³⁶⁻³⁸. However, significant increase in intraocular pressure has been a major problem with these injections in subsequent trials³⁹⁻⁴¹.

ANTI-VEGF TREATMENT

VEGF is an important mediator of angiogenesis in AMD and is a validated therapeutic target. Inhibitors of angiogenesis have been a recent advance in the treatment of wet AMD. These agents do not appear to cure the condition. Rather, they halt or slow progression of AMD in most cases. The drugs currently used are Macugen, Lucentis and Avastin.

Macugen

The first to enter the marketplace was pegaptanib sodium, a 28-base anti-VEGF aptamer, which antagonizes the specific amino acid isoform 165 when administered intravitreally, and blocks new blood vessel growth. The pivotal study with pegaptanib sodium was the multicenter VEGF Inhibition Study in Ocular Neovascularization (VISION trial) which enrolled 1190 patients²². Intravitreal injection every 6 weeks slowed the loss of vision associated with neovascular AMD. The study included all lesion subtypes: predominantly classic, minimally classic, and occult with no classic CNV. It is the first anti-VEGF drug approved for the treatment of ocular disease and for intravitreal use. Its introduction was followed closely by the emergence of two other more effective VEGF inhibitors: ranibizumab and bevacizumab.

Lucentis

Ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA)

is the second to be approved for the treatment of AMD-associated CNV. It is an antibody fragment derived from a murine antibody to VEGF that specifically binds all active isoforms of VEGF. The results of large, prospective clinical trials of intravitreal injections of ranibizumab have shown promising results with improvement of vision occurring in approximately 40% of patients^{23,42}. It is the first treatment for neovascular AMD that not only prevented visual acuity loss but also improved visual acuity in large numbers of patients in Phase III clinical trials²³. The main published study with ranibizumab (Minimally Classic/Occult Trial Age-Related Macular Degeneration, or MARINA) was a two-year, phase III trial designed to evaluate monthly injections in 716 patients with minimally classic or occult with no classic lesions. All of these patients had recurrent disease. They were randomized 1:1:1 to receive either sham injections (n = 238), or injections of ranibizumab at 0.3 mg (n = 238) or 0.5 mg (n = 240). At 12 months, at least 94% of patients in both arms receiving ranibizumab lost fewer than 15 letters, compared with 62% of patients in the sham treatment arm. Further, at 24 months, 25% of patients in the 0.3 mg ranibizumab arm, and 34% of patients in the 0.5 mg ranibizumab arm, showed a gain in VA of at least 15 letters, regardless of lesion type or size, or baseline VA. The gain in vision was evident within seven days of the first injection.

The next study (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; ANCHOR) compared the same two dosage strengths of ranibizumab against V-PDT in 423 patients who were followed out to 12 months²³. At that point, patients in the ranibizumab 0.5 mg arm gained, on average, 11.3 letters, while patients in the V-PDT arm lost, on average, 9.5 letters, for an overall difference in treatment effect of 20.8 ETDRS letters. The outcomes were more or less similar at month 24. In addition, approximately 95% of patients in both ranibizumab arms lost fewer than 15 letters, while 35% and 40% of patients in the 0.3 mg and 0.5 mg arms respectively gained more than 15 letters compared with patients who were treated with V-PDT. Interestingly, a sub-group analysis reported that as lesion size increased, the benefit of ranibizumab 0.5 mg became less significant when compared with V-PDT. Adverse events noted with ranibizumab included local injection site and ocular inflammation, transient spikes in intraocular pressure, arteriothrombotic events such as nonfatal myocardial infarction or stroke, and death from other vascular causes.

OCT formed the basis for retreatment in the recently published PrONTO (Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with intra-Ocular ranibizumab) study⁴³. In this trial, 40 patients received ranibizumab 0.5mg at baseline, and then again at months 1 and 2. Additional treatment was given only if there was a loss of ≥ 5 ETDRS letters, or an increase in macular thickness of at least 100 microns, continued subretinal fluid detected by OCT after one month, new hemorrhage, and new neovascularization. Results were encouraging in terms of reduced retinal thickening, and improved VA, and OCT-guided retreatment protocols have become widely adopted in clinical practice since then.

In another study⁴⁴, (A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration; PIER), the transition to less frequent therapy was associated with increased central retinal thickness on OCT, as well as increased CNV leakage on FA. Although quarterly ranibizumab therapy in the PIER Study maintained baseline VA, it was associated with a 4.5-letter decline in the maximal VA benefit achieved during the initial "induction" period of therapy. It is possible that the return of retinal edema contributed, at least in part, to the decline in the maximal VA benefit achieved. Keane et al provided

additional evidence that some patients with neovascular AMD may require more frequent ranibizumab injections to control CNV leakage and OCT features of exudation⁴⁵.

Avastin

Bevacizumab (Avastin; Genentech Inc.) is a humanized monoclonal antibody (derived from the same murine antibody as ranibizumab) that also specifically binds all biologically active isoforms of VEGF like pegaptanib. Ranibizumab, also developed by Genentech, is significantly more costly, but any greater efficacy remains to be proven. Ranibizumab is thought to have a greater binding affinity for VEGF owing to its smaller molecular weight. Bevacizumab is approved by the Food and Drug Administration for the treatment of advanced colorectal cancer in combination with 5-fluorouracil⁴⁶. Recently, systemic administration of bevacizumab was evaluated in patients with neovascular AMD, and demonstrated improved visual acuity and reduced retinal thickness⁴⁷. Published studies involving patients treated with 1.25 mg Bevacizumab injections spaced one month apart, have demonstrated significant improvements in retinal thickness in as little as one week after the first injection, and significant improvements in VA²⁴ at three months. Such improvements appear to be sustained over several months. There is, however, a small but significant risk of thromboembolic events, such as stroke and myocardial infarction with systemic administration⁴⁸. Therefore, intravitreal administration of bevacizumab is attractive to reduce systemic exposure. Subsequently, numerous reports of intravitreal injection of bevacizumab in patients with CNV from AMD have shown rapid reduction of neovascular leakage^{24,49}.

VEGF Trap-Eye

VEGF Trap (Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA) is a recombinant protein in which the binding domains of VEGF receptors 1 and 2 are combined with the Fc portion of immunoglobulin-G. The receptor portion of the molecule has a high affinity for all VEGF-A isoforms (Kd<1 pM), placental growth factors 1 and 2, and VEGF-B⁵⁰. Therefore, VEGF Trap is distinguished from ranibizumab by its higher binding affinity for all VEGF-A isoforms and its ability to inhibit other VEGF family members. It also binds VEGF more tightly than all other anti-VEGF agents.

The Clinical Evaluation of Anti-angiogenesis in the Retina (CLEAR) study was a randomized, double-masked, ascending dose, placebo-controlled phase I trial of 18 patients with neovascular AMD who received either placebo or 1 of 3 systemic doses of intravenous VEGF trap (0.3, 1.0, and 3.0 mg/kg)⁵¹. The study found a dose-dependent increase in systemic blood pressure, which was clinically significant above the 1.0 mg/kg dose and further studies of systemic VEGF trap were halted. CLEAR IT-1 was a phase I dose escalation study of a single intravitreal injection of multiple doses VEGF trap (0.05, 0.15, 0.5, 1, 2, and 4 mg). At 6 weeks, mean gain in visual acuity was 4.8 letters and mean OCT central retinal thickness decreased from 298 to 208 μ m. The potential benefit of VEGF trap is a sustained effect compared to single injections of other VEGF-binding agents, although this has not been demonstrated in a head-to-head trial. A phase II VEGF trap study (CLEAR-AMD) is currently in the process of enrolling patients.

In a phase I Study of Intravitreal VEGF Trap-Eye in patients with neovascular AMD, intravitreal injection of up to 4 mg of VEGF Trap-Eye was well tolerated with no evidence of ocular inflammation⁵². Several patients, especially those receiving 2 or 4 mg of VEGF Trap-Eye, showed substantial improvement in BCVA associated with reductions in foveal thickness. Phase III trials to investigate the efficacy of intraocular VEGF Trap-Eye in patients with NVAMD are under way.

The rationale of repeated injections, interval between injections, any retinal toxicity and long-term effects of VEGF Trap-Eye in CNV are some of the questions being addressed in ongoing clinical trials.

VEGF RECEPTOR TYROSINE KINASE INHIBITION

A further method of inhibiting the effect of increased VEGF within the eye with CNV is to inhibit the tyrosine kinase activity of VEGF receptors. Vatalanib[®] (formerly PTK-787, Novartis International AG, Basel, Switzerland) is a potent inhibitor of all known VEGF receptor tyrosine kinases, VEGFR1 (sFlt-1), VEGFR2 (KDR), and VEGFR3 (Flt-4). Its satisfactory oral bioavailability makes it an attractive alternative to intravitreally or intravenously injected medications⁵³. The Study of Vatalanib and Photodynamic Therapy with Verteporfin in Patients With Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-related Macular degeneration (ADVANCE) is currently enrolling for a phase I/II comparison of PDT to PDT/vatalanib.

COMBINATION THERAPY

A two-component model of CNV has been developed to offer a conceptual framework to structure combination treatments^{54,55}. The first vascular component, composed of vascular endothelial cells and associated pericytes, arises through the interaction of a number of growth factors such as VEGF and platelet-derived growth factor (PDGF), which maintains pericyte viability. This vascular component of CNV can be selectively targeted with anti-VEGF and anti-PDGF drugs or nonselectively with such modalities as ionizing radiation. The second nonvascular component is the remaining cells, such as the inflammatory cells, glial cells, myofibroblasts, and fibrocytes. This component can be targeted selectively by inhibiting specific cytokines such as tumor necrosis factor α or nonselectively with antiinflammatory drugs such as corticosteroids. Because of mutual interactions between the two components, inhibiting one has the potential to at least partially inhibit the other. Blocking the extravascular component and its products, such as scar formation, may help reduce disease morbidity in CNV as well.

Current theories suggest that pericyte coverage provides survival signals to neovascular endothelial cells and hence makes them resistant to VEGF withdrawal. Anti-PDGF treatment strips away pericytes to leave the endothelial cells unprotected and vulnerable to anti-VEGF treatment. Combination of anti-VEGF and anti-PDGF has been shown to produce inhibition and regression of CNV compared with anti-VEGF treatment alone⁵⁶.

Encouraged by these facts, the safety of anti-PDGF drug E10030 is being tested in combination with ranibizumab in a Phase I study.

Several other studies are combining therapeutic modalities, including the BRIDGE study (ranibizumab plus anecortave acetate), PROTECT study (ranibizumab plus PDT with verteporfin), VISION phase IV study (pegaptanib plus PDT) are currently underway.

The interaction between the transmembrane integrin α 5 β 1 receptor and its natural ligand, fibronectin in the angiogenic cascade is critical to endothelial cell survival. Inhibiting this interaction may disrupt the process of neovascularization⁵⁷. One such agent, Volociximab (M200), is undergoing a phase one trial in combination with Ranibizumab⁵⁷.

Therapies such as ARC 1905 are directed at complement activation and are undergoing trials in AMD⁵⁷. These combination therapies may be effective in preventing AMD from occurring or stopping AMD at a very early stage.

Attempts to target retinal and choroidal new vessel formation using the small molecule inhibitor carboxyamidotriazole (CAI), known for its anti-angiogenic and anti-tumor effect support the potential of developing it for treatment of proliferative retinopathies in humans such as proliferative diabetic retinopathy, exudative AMD, and retinopathy of prematurity⁵⁸.

CCR3 is a target for AMD diagnosis and therapy⁵⁹. Eosinophil/mast

cell chemokine receptor CCR3 is specifically expressed in choroidal neovascular endothelial cells in humans with AMD, and that despite the expression of its ligands eotaxin-1, -2 and -3, neither eosinophils nor mast cells are present in human CNV. CCR3 blockade has been found to be more effective at reducing CNV than VEGF-A neutralization. CCR3 targeting might reduce vision loss due to AMD through early detection and therapeutic angioinhibition because in vivo imaging with CCR3-targeting quantum dots located spontaneous CNV invisible to standard FA in mice before retinal invasion.

Bevasiranib (formerly Cand5, Acuity Pharmaceuticals, Philadelphia, PA) is the first small interfering RNA agent developed for the treatment of neovascular AMD and has been reported safe by preclinical and clinical research⁶⁰. Injected intravitreally, it acts by inducing catalytic destruction of messenger RNA to silence gene expression and targets the production of VEGF protein. It does not affect existing VEGF protein, suggesting that it may offer a synergistic effect when given in combination with anti-VEGF treatments, such as ranibizumab.

TRIPLE THERAPY IN AMD

AMD is the product of several interrelated pathogenic processes. Augustin and colleagues have reported some success by combining bevacizumab, V-PDT, and the steroid dexamethasone into a "triple therapy regimen" that attacks CNV through three different mechanisms⁶¹. The regimen was well tolerated and the benefit was observed across all lesion types⁶². V-PDT eradicates existing neovascularization. Bevacizumab, prevents the growth of new blood vessels in the eye. And finally, besides being an anti-inflammatory, the corticosteroid dexamethasone has anti-angiogenic properties and antifibrotic and anti-permeability characteristics, which help preserve the integrity of the blood-retinal barrier. Augustin's triple therapy regimen offers another attractive alternative for treatment, because it relies on three different mechanisms of action: eradicating existing CNV (vaso-occlusive), preventing new CNV (anti-angiogenic), and countering the inflammatory process.

Combination therapy has several prospective goals: improved outcome, less frequent or invasive treatment, and fewer complications.

ANECORTAVE ACETATE

Anecortave acetate has also been used in patients with AMD-related CNV, producing similar visual acuity results to PDT with verteporfin in the C-01-99 study⁶³. With improved therapies and outcomes, anecortave acetate is not appropriate monotherapy for active CNV. However, the NEI is sponsoring the BRIDGE study that will evaluate combination therapy of anecortave acetate and ranibizumab.

OTHER TREATMENT STRATEGIES

Besides small interfering RNA, anecortave acetate, and vatalanib (receptor tyrosine kinase inhibitors), Squalamine lactate (Evizon[®], Genaera Corporation, Plymouth Meeting, PA) is another treatment that decreases the effect of VEGF⁶⁴. It inhibits plasma membrane ion channels with downstream effects on VEGF, and has shown promising results with systemic administration. However, Genaera has abandoned this product and is no longer in clinical development.

The advent of antiangiogenic therapies has revolutionized the management of neovascular AMD in recent years. Although visual function and quality of life are the most important and primary outcome parameters in these clinical studies, imaging findings have been advocated as important secondary outcome variables to confirm the biological efficacy of these various therapeutic strategies.

ROLE OF IMAGING

In parallel with these advances, OCT has evolved into an important diagnostic tool in the management of patients with macular diseases⁶⁵.

Until the advent of OCT, classifying the AMD phenotype was limited to evaluation by color photos, FA and fundus autofluorescence. OCT is an outstanding tool for assessing effects of drugs on CNV because it provides an objective measure of the amount of fluid within or under the retina. Clinical OCT units are reasonable in identifying retinal thickness in eyes with a normal PR-RPE interface; however, current time-domain OCT (TD-OCT) imaging is limited when attempting to image focal disease changes at the PR-RPE interface. Spectral domain OCT (SD OCT) provides superior resolution and image quality of PR changes compared with standard TD-OCT.

The most common imaging outcome parameters in recent AMD trials include the area and greatest linear dimension of choroidal neovascular lesions and retinal thickness as calculated using OCT^{65,66}. A number of studies have utilized SD OCT in assessing and monitoring quantitatively the various treatment responses in neovascular AMD⁶⁷⁻⁷⁰.

3D OCT provides realistic anatomic maps of retina, RPE, and retinal thickness in AMD patients. FA-OCT overlay images help in discriminating between the predominant CNV lesion types. Their precise shape can be identified, together with information about the lesion localization and leakage activity.

RADIATION TRIALS IN AMD

Radiotherapy is a promising adjunctive tool to antiangiogenesis therapies for control of CNV in AMD. A variety of radiotherapy types, including external beam radiation, brachytherapy, and proton beam have been tried so far⁷¹. Newer techniques such as pretreating neovascular tissue to increase its sensitivity to radiation, thereby reducing the energy dose have been developed to improve efficacy. These are intended to provide precise energy delivery, so that tissue destruction remains confined to the target.

In a recent report of combination treatment of CNV using radiotherapy and bevacizumab, results were excellent, with 76% of patients gaining at least 10 letters of visual acuity⁷². Of responders, most required no more than one additional injection of bevacizumab over the first year of follow-up. No patient over this period developed any evidence of radiation retinopathy or other radiation-related complications. On the basis of those results, a Phase 3 study has been initiated with enrollment completed.

SURGICAL TREATMENT

Submacular surgical removal of CNV⁷³, pneumatic displacement of large subretinal haemorrhage⁷⁴, and macular translocation⁷⁵ have been tried for AMD associated with CNV, but none of these therapies has proven effective to be appropriate primary treatment strategies for AMD-associated CNV.

NEW TARGETS IN AMD

As more is understood about the pathogenesis of AMD, it will be important to target other contributors to vision loss. For example, subretinal fibrosis, which is a significant impediment to recovery of vision after medical therapy in wet AMD, may be responsive to a combination of antiintegrins with an anti-VEGF drug. The final goal is to treat not only the immature neovascularization but also the mature vessels. The ultimate goal is to preserve sight for a long term.

Fibrosis is an important additional target to enhance the benefits of VEGF inhibitors in the treatment of AMD. Several strategies such as integrin antagonists, inhibitors of mammalian target of rapamycin, vascular-disrupting agents, and radiation have reached or are near clinical trials. Although none targets fibrosis specifically, each inhibits a process relevant to eventual fibrosis formation. Palomid 529, a mammalian target of rapamycin inhibitor has demonstrated a strong antifibrotic effect in retinal fibrosis models. A vascular-disrupting agent called combretastatin A4P (CA4P) has been evaluated in a

Phase I study in humans with myopic macular degeneration, where it demonstrated relatively modest effect, but the characteristics of AMD may be more suitable for its activity.

Control of atrophy, which is generally observed at an earlier stage of AMD progression than fibrosis, is another potential target for improving outcome. The candidate targets for preventing atrophy include neurotrophic factors, free radical scavengers, and retinobinding competitors. Complement inhibition may be another viable strategy.

ROLE OF NANOTECHNOLOGY

Nanotechnology involves using nanoparticles (NPs) which are microscopic particles whose size is on the nanometer scale⁷⁶. These NPs show considerable promise for drug delivery to the retina, for gene therapy, and for powering prosthetic "artificial retinas". They can be synthesized with organic, inorganic polymers or a combination of both polymers in various molecular sizes and conformations allowing for encapsulation of specifically adapted formulations. Also, they can be made biodegradable. These properties of NPs have encouraged research into their possible application in the treatment of AMD by continuous intraocular drug release through coupling the desired drugs to liposomes, microparticles (1–1000 µm) or nanoparticles (1–1000 nm, generally 20–300 nm).

Nanotechnology may offer several advantages for administration of drugs in vivo, such as controlled release, injectable and sterilizable formulation, and long shelf-life after lyophilization. In addition, drugs and genetic materials embedded or encapsulated into the NPs can be protected from immediate dilution and degradation and also overcome drug solubility issues. In AMD, the side-effects resulting from multiple intravitreal injections of anti-VEGF drugs can not be ignored. NPs may be used to deliver these drugs for sustained release in a longer time period, which may reduce the frequency of intravitreal injection. In addition to delivering chemical drugs, nanoparticle-mediated gene delivery has also emerged as a promising tool for gene therapy strategies.

HORMONE THERAPY

There are few reports of role of hormone therapy on AMD⁷⁷⁻⁷⁹. Treatment with conjugated equine estrogens (CEE) or with CEE combined with progestin (CEE+P) does not affect early stage AMD, but treatment with CEE+P may reduce the risk of soft drusen or neovascular AMD⁷⁹.

FUTURE TREATMENT POSSIBILITIES

Another target of angiogenesis has been through non-VEGF pathways, including bioactive lipids. Sphingomab (Lpath Inc., San Diego, CA) is a monoclonal antibody targeted against sphingosine-1-phosphate, which has been implicated in angiogenesis, scar formation, and inflammation⁸⁰.

Encapsulated Cell Technology (ECT), developed by Neurotech, Lincoln, RI, involves implantation of a small semi-permeable polymer capsule into the vitreous cavity.

The capsular implant is lined with cultured cells that have been engineered to secrete certain proteins or peptides. The initial studies of ECT in humans have been phase I trials of ECT containing modified human retinal pigment epithelial cells (ARPE-19), programmed to secrete ciliary neurotrophic factor (CNTF) in the treatment of retinitis pigmentosa and non-neovascular AMD^{81,82}. Assuming that these capsules demonstrate immune privilege, ECT allows for theoretically sustained low-dose delivery of a single or combination of proteins or other cellular products into the vitreous cavity. Rather than

replacing specific defective genes or supplying deficient proteins, some have advocated replacing entire cell lines and tissues. Although not yet ready for human trials, stem cell transplantation and RPE transplantation are enticing goals for the management of chronic blinding diseases⁸³.

SUMMARY

During the past four decades there have been some highly encouraging improvements in the management of CNV secondary to AMD. Early treatments like laser photocoagulation prevented the rapid spread of CNV, but often led to some degree of permanent vision loss. V-PDT arrested the progress of the disease and even improved visual acuity for a small percentage of patients. Anti-angiogenic agents (VEGF inhibitors) now offer improvements in visual acuity for at least one-third of patients. Anti-VEGF drugs are among the most effective therapies for AMD but the underlying process of AMD is not limited to new vessel formation. Apart from VEGF, many other anti-angiogenic factors exist and may be rewarding targets of future studies. The development of additional treatments to provide more effective disease control may depend on addressing several pathophysiologic processes simultaneously. The search for more effective treatments will require a better understanding of the different physiologic processes involved with this disease process.

Prevention of AMD includes lowering risk factors and eating healthy diets of antioxidants and zinc. Quit smoking and eating foods with Vitamins A, C and E could help reduce chances of developing AMD. Exercising and keeping healthy are always good preventive methods for all diseases.

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