Pathogenesis of Retinal Disease

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THE PATHOGENESIS OF RETINAL DISEASE

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Target Audience: Retina Specialists and Ophthalmologists

Activity Description: The goal of this CME-accredited symposium and supplement is to improve clinical knowledge of current research and emerging science on the pathogenesis and multifactorial nature of retinal disease. In order for retinal surgeons to provide optimal patient care based on evidence-based medicine for the management of retinal diseases, it is critical that they understand the role of genetics, inflammation, hypoxia, and cytokines in various retinal disease states, as well as the additional impact of underlying systemic disease. Important in this medical education project will be improving surgeon understanding of the clinical implications based on the different pathological mechanisms of retinal disease.

Statement of Need: Given the current and predicted impact of poor health in our aging society, a significant burden exists for physicians to remain aware of current and emerging clinical science that impacts their patients. One area of recent and continued interest in the field of ophthalmology is the development of new treatment strategies for retinal vascular occlusive disease.

Learning Objectives: Upon completion of this activity, the participant should be able to:

- Describe current and future epidemiology of retinal disease-including the impact of systemic disease and comorbidities
- Discuss the pathogenesis of retinal disease and the contributions of genetics, inflammation, hypoxia, and cytokines in development of disease
- Review current and emerging data describing the various treatments that target the contributing factors in the cascade of retinal disease
- Discuss therapeutic targets in retinal disease (eg, AMD and RVO) based on the current understanding of the parts played by genetics, inflammation, hypoxia, and cytokines
- Identify the importance of evidence-based medicine and clinical trial design in clarifying retinal disease treatment

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Accreditation: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The National Retina Institute (NRI) and Retina Today. NRI is accredited by the ACCME to provide continuing medical education for physicians.

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Tyrosine Kinase Inhibition

A complete shut down of the neovascularization pathway is the goal.

BY DAVID M. BROWN, MD

Neovascularization is an intricate process in which abnormal blood vessels grow as a response to vascular endothelial growth factor (VEGF) or downregulation of platelet-derived growth factor (PDGF). An analogy can be made from how neovascularization is powered to the power source of a car engine. There are promoters (gas pedal) and inhibitors (brake pedal). In a car, the gas pedal initiates the fuel injector, which operates on downstream processing, turning on the engine. Currently the only tools that we have to turn off the “gas” in the neovascularization process are anti-VEGF agents such as ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech). These agents act in a similar manner to a clogged injector by preventing fuel from reaching the injector; however, there are other “injectors” that are permitted to fire, allowing the signal cascade to continue, albeit in a hindered manner.

KINASE INHIBITORS

The power supply for VEGF is adenosine-tri-phosphate (ATP). If ATP could be blocked, would the entire neovascularization process shut off? In an effort to answer this question, there has been a significant amount of pharmaceutical development looking at tyrosine kinase inhibitors, which are theorized to be capable of blocking ATP, inhibiting the pathway completely, and shutting down this process.

Neovascular AMD is characterized by choroidal neovascularization (CNV) that enters the subretinal space. Aberrant activation of growth factor receptors is a driving force in the growth of many of these blood vessels. As the specific ligand (VEGF, PDGF) binds to its receptor through ATP phosphorylation, a signaling cascade is initiated leading to the pathogenesis of neovascular AMD (Figure 1).

Tyrosine kinase inhibitors have the ability to hinder multiple pathways including inflammation and angiogenesis.

PKC412 (Novartis, Inc.) is a kinase inhibitor for diabetic macular edema. In early clinical studies by Campochiaro et al, oral PKC412 proved to be anatomically effective, but caused hepatotoxicity, suggesting that local delivery would be more advantageous.

My colleagues and I have evaluated another experimental eye drop that is a pro-drug and kinase inhibitor. TG100801 (previously owned by Targegen, which has been acquired by Sanofi-Aventis) is a highly selective kinase inhibitor, which is metabolized by esterases in the eye and converted to TG100572. TG100572 has shown to be a potent inhibitor of kinases that regulate inflammation, angiogenesis, and vascular leak, such as VEGF receptors (VEGFR), PDGF receptors (PDGFR), fibroblast growth receptors, Ephrin receptors, and Src family kinases. In animal models, this drug appears to be...
better than bevacizumab in terms of preventing leakage. In a laser-induced CNV model, the inhibition appears to be dose dependent.

What happens when TG100801 is applied to humans? We had a patient with subretinal fluid and a pigment epithelial detachment (PED; Figure 2A). After one drop TG100801, the fluid had regressed (Figure 2B) but the PED remained (Figure 2C). We observed on the slit lamp that red, electrostatically charged particles had formed on the cornea upon instillation, which had no effect on visual acuity.

Another kinase inhibitor that is currently under evaluation for retinal disease is pazopanib (GlaxoSmithKline). Pazopanib is a multitargeted tyrosine kinase inhibitor that works via activation of VEGFR, PDGFR, and c-kit receptors to trigger the tyrosine kinase cascade, leading to changes in cellular behavior to prevent VEGF-induced permeability and angiogenesis.

Further research is required for all of these aforementioned tyrosine kinase inhibitors, and one or more may prove promising. Currently, however, there is no one agent that has “knocked our socks off.”

SUMMARY

Targeting the “fuel injector” of neovascularization (tyrosine kinase) appears to make sense. There is some initial anatomic validation to tyrosine kinase inhibition, but the devil lies in the details. Whether this route is the answer that will help change the way we treat retinal disease in the future is yet to be determined.


Molecular Targets for Retinal Diseases

Hypoxia-regulated genes play an important role in vascular permeability and neovascularization.

BY PETER A. CAMPOCHIARO, MD

One of the long-standing observations in ophthalmology is that there is a high correlation between retinal nonperfusion and neovascularization—when there is substantial dropout of the retina vessels, retinal neovascularization occurs.

We now understand that hypoxia-inducible factor-1 (HIF-1) is the main protagonist in this process. HIF-1 is a transcription factor that under normoxic conditions is hydroxylated, binds to the Von Hippel-Lindau (VHL) protein and is rapidly degraded. In the setting of hypoxia, however, it is stabilized and translocates to the nucleus where it binds to the hypoxia response element, which increases transcription of a whole host of genes.

VASCULAR ENDOTHELIAL GROWTH FACTOR

One of the most important hypoxia-regulated genes is vascular endothelial growth factor (VEGF). Mouse retinal vessels do not develop until after birth. Right after birth, the retinal vessels begin to develop at the optic nerve and grow out to the periphery of the retina, a process driven in part by VEGF. If infant mice are put into a hyperoxic environment, HIF-1 is destabilized and degraded and the expression of VEGF is significantly reduced (Figure 1). The development of retinal vessels ceases and the newly developed vessels, which are dependent upon VEGF for survival, regress. After 5 days in a high-oxygen environment, there are large areas of nonperfused retina and return of the mice to room air results in retinal ischemia. This results in stabilization of HIF-1, increased production of VEGF, and retinal neovascularization.

In choroidal neovascularization (CNV), the blood vessels grow under the retina and so it is not clearly related to hypoxia (Figure 2). To determine if VEGF plays a role in that we tried to mimic that disease process by creating transgenic mice using the rhodopsin promoter (rho) to express VEGF in photoreceptors (Figure 3).1 The rho/VEGF transgene begins production of VEGF at postnatal day (P) 7. By P10 the endothelial cells begin to migrate into the photoreceptor layer and at P21, well-developed blood vessels that extend from the deep capillary bed into the subretinal space are visible (Figure 4). The hyperfluorescence represents significant neovascularization with feeder vessels from the deep capillary bed extending into the subretinal space forming clusters of new vessels partially surrounded by retinal pigment epithelial cells (Figure 5). After longer periods of time, these blood vessels form an extensive complex of vessels in

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Figure 1. In situ hybridization for VEGF shows marked decreased expression in the retina during hyperoxia and marked increase during hypoxia.
the subretinal space. Fluorescein angiography shows hyperfluorescent spots beneath the retina that increase in size over time (Figure 6), similar to what is seen in human patients with neovascular age-related macular degeneration (AMD). Because the new vessels extend from retinal vessels into the subretinal space, this is actually a model for retinal angiomatous proliferation (RAP). In order to get new vessels that grow from the choroid into the subretinal space, it is
necessary to perturb Bruch’s membrane. One way to achieve this is to rupture Bruch’s membrane with laser photocoagulation, which results in CNV (Figure 7).

VEGF TRAP

VEGF trap is a recombinant protein consisting of VEGF-binding domains from VEGF receptors 1 and 2, which binds VEGF-A and placental growth factor, both hypoxia-regulated gene products. Administration of VEGF trap strongly suppresses laser-induced CNV indicating that VEGF and possibly placental growth factor are critical stimuli in this model.

PDGF-B

Another hypoxia-regulated gene is platelet-derived growth factor B (PDGF-B). While VEGF is a survival factor for newly developed endothelial cells, PDGF-B is a survival factor for newly developed pericytes. The pericytes provide survival factors other than VEGF to endothelial cells. Elimination of pericytes makes endothelial cells more dependent upon VEGF for survival. We made transgenic mice with inducible expression of PDGF-B; their phenotype is similar to that of mice with inducible expression of VEGF in the retina; both develop severe neovascularization and retinal detachment. Compared to agents that target only VEGF, kinase inhibitors that block both VEGF and PDGF receptors are more effective inhibitors of CNV. PKC412 is a nonselective VEGF and PDGF inhibitor that strongly suppresses CNV (Figure 8). Pazopanib is another kinase inhibitor that blocks both PDGF and VEGF receptors. Unlike specific VEGF antagonists, which only suppress CNV, pazopanib causes regression of established CNV (Figure 9).

SDF-1

SDF-1 and its receptor, CXCR4, are hypoxia-regulated genes. CXCR4 is located on monocytes and macrophages and is involved in macrophage recruitment from the bone marrow and blood stream into tissues. In ischemic retina, both SDF-1 and CXCR4 are increased. Even in the absence of ischemia, elevated levels of VEGF cause increases in SDF-1 and CXCR4. Under normal conditions, there is very little SDF-1 in the retina, while in hypoxic retina, it is produced by glial cells identified by staining for glial fibrillary acidic protein. The production of SDF-1 by glial cells promotes influx...
edema while on supplemental oxygen (Figure 13) and nine eyes of patients DME experienced a reduction in thickening (Figure 12B), there is a marked decrease in thickening of the retina. After 3 months of supplemental oxygen patient, showing thickening throughout the central area by nasal cannula.9 Figure 12A is a baseline OCT from one macular edema (DME) continuous supplemental oxygen performed a study where we gave patients with diabetic retinal hypoxia in macular edema, my colleagues and I permeability and macular edema? To investigate the role of neovascularization. Does it play a role in excessive vascular permeability? Which of the hypoxia-regulated gene products is most important in macular edema? Not surprisingly, it is VEGF. Injecting a pellet that releases VEGF into the vitreous cavity of monkeys (Figure 14A) results in tremendous leakage from the retinal vessels (Figure 14B).10 VEGF antagonists provide great benefit in macular edema due to DME or retinal vein occlusions.

**SUMMARY**

Hypoxia-regulated genes play an important role in ocular neovascularization and macular edema. VEGF is particularly important and most efforts thus far have been directed at suppressing VEGF. Over the next several years agents that target other hypoxia-regulated gene products will be tested in combination with VEGF antagonists to see if additional benefit can be obtained.

Clinical Trials in AMD and RVO

A review of the data regarding clinically available therapies and those on the horizon.

BY DANTE PIERAMICI, MD

In recent years, numerous retinal disease-related clinical trials have been completed, particularly concerning age-related macular degeneration (AMD) and retinal vein occlusion (RVO).

Today’s “standard care” for treating AMD is based primarily on two phase 3, randomized clinical trials, MARINA and ANCHOR, that evaluated intravitreal ranibizumab (Lucentis, Genentech).

The primary endpoint of these studies was visual stabilization, defined in these trials as losing fewer than three lines of visual acuity. Ranibizumab was found to be far superior to sham injection and photodynamic therapy (PDT) in these studies.

The most interesting finding from these studies was that on average, patients experienced visual gains with ranibizumab. Prior to these data, we thought that the only way we could achieve good vision in patients with AMD was to prevent the occurrence of neovascularization. Clearly, from a pathologic standpoint there is a period of time when reversible changes are present and the timely correction can lead to vision improvement.

**REDUCED DOSING FOR AMD**

**PIER.** The PIER trial evaluated a fixed reduced schedule. Patients had three monthly treatments and then were treated on a quarterly basis out to the primary endpoint of 12 months. Although the results at month 12 were better than sham, the results were not as good as they were in MARINA and ANCHOR (Figure 1).

**PRONTO.** The PRONTO trial evaluated as-needed (PRN) therapy with ranibizumab. In PRONTO, patients were treated with three mandated initial monthly injections, after which they received PRN injections based on the criteria of five or more letter loss of vision from the last visit, persistent or recurrent fluid on OCT, an increase in central retinal thickness (CRT) of more than 100 µm, or new hemorrhage. PRONTO set a relatively low threshold for retreatment, and the outcomes were good and comparable to what was seen in MARINA/ANCHOR at 1 year (Figure 2). It is important to note, however, that there were only 40 patients enrolled in PRONTO, compared with 716 in MARINA and 423 in ANCHOR.

**HORIZON.** What other data do we have for PRN treatment? The HORIZON trial was an extension trial of the...
patients in the MARINA, FOCUS, and ANCHOR trials. The patients who did not receive ranibizumab in the original trials could now crossover to intravitreal ranibizumab treatment in HORIZON. Relatively few injections were given to patients during the 2 years in HORIZON. Sixty-two percent of patients in the initially treated group received zero to three injections and 58% of patients in the crossover group received zero to three injections. Through 24 months of HORIZON, the mean and median number of injections in the ranibizumab treated-initial group was 3.6 and 2.0, and for the treated-crossover group, the mean and median was 4.2 and 3.0.

As you can see, when they were in the fixed period in the original trials, patients treated with ranibizumab did well. When they went into the PRN dosing phase in HORIZON, however, the initial visual acuity gains appeared to fade over time (Figure 3). The main question that these results raised was whether this is the natural course after 2 years of continued treatment or whether these patients received inadequate dosing. The results of the HORIZON trial did provide insight into the pathophysiology of patients who were not treated in the first 2 years of the initial trial. For the crossover patients, there was little visual improvement during their treatment in HORIZON, which suggests that the window of opportunity for reversible vision loss had passed. However, these patients may have continued to lose more vision had they not received this treatment.

SAILOR. SAILOR was another trial that evaluated PRN dosing. In this trial, over 1,000 patients in each arm were randomized to either 0.3 mg or 0.5 mg ranibizumab. Patients had three monthly injections and then PRN injections as determined at follow-up visits at intervals of 3 months. The bar for retreatment for SAILOR was set fairly high: at least one line of visual acuity loss or an increase in CRT of 100 µm.

During the monthly treatment period there were improvements in visual acuity but much of this was lost in them PRN dosing period (Figure 4). Whether a more liberal retreatment regimen with closer follow-up would have improved the results is probable. However, whether any PRN dosing regimen can equal the results of monthly dosing is uncertain and we await the results of the CATT trial, which should help clarify this issue.

A BETTER DRUG FOR AMD?

To date, the preponderance of data suggests that to guarantee good outcomes while treating neovascular AMD, monthly injections of ranibizumab is the most rational approach. I do think, however, that a PRN treatment schedule can produce similar results if the threshold for retreatment is low and patients are evaluated monthly. A treat-and-extend approach may also be an alternative and is employed by many to identify subgroups of patients who may need less frequent treatment and follow-up. Investigational approaches to improving the duration of
treatment will employ higher dosages of ranibizumab, extended release of the drug, higher affinity molecules, and the use of combination therapies.

**CLEAR-IT 2.** VEGF-trap is one drug that might provide increased duration of effect and efficacy over ranibizumab, as it has higher affinity binding for VEGF. VEGF-trap also blocks placental growth factor, which may provide additional benefits.

The phase 3 data for VEGF-trap are still under evaluation, but the phase 2 data (CLEAR-IT 2) suggested increased durability over ranibizumab (Figure 5). The two phase 3 studies, VIEW 1 and VIEW 2, are currently fully enrolled and underway. In these trials, patients are randomized 1:1:1:1 to either 0.5 mg VEGF-trap every 4 weeks, 2.0 mg VEGF-trap every 4 weeks, 2.0 mg VEGF-trap every 8 weeks, or 0.5 mg ranibizumab every 4 weeks.

**COMBINATION THERAPIES**

If A works and B works and A and B work differently, is it reasonable to conclude that A+B will work best? This is the reasoning behind any combination therapy and is well documented in oncology and infectious disease management. Photodynamic therapy (PDT) was one of the first adjunctive therapies that we evaluated in combination, as it had already proved to be safe for patients. Additionally, PDT appears to have a different mechanism of action than ranibizumab or steroids. In theory, it selectively targets and accumulates in abnormal vessels. Activation with laser leads to angio-occlusion of the choroidal neovascularization. Anti-VEGF therapy works primarily by reducing vascular leakage and closing early neovascularization. PDT offers the possibility of closing more mature larger caliber neovascularization, perhaps reducing the chance for recurrence.

**MONT BLANC.** There are a number of clinical trials evaluating ranibizumab on combination with PDT. The MONT BLANC randomized patients to combination therapy (ranibizumab plus standard fluence PDT) or monotherapy with ranibizumab. Patients had a fixed dosing for the first 3 months in both groups received three ranibizumab injections. One group also received standard fluence PDT and then was treated on a PRN basis during the maintenance period. There was no statistically significant difference in visual outcome between the two groups (Figure 6), although the combination group seemed to do slightly worse. Interestingly, there was no significant difference in the number of retreatments and the number of injections, suggesting that PDT had no effect on reducing the number of treatments with ranibizumab.

**RADICAL.** The RADICAL trial investigated triple therapy (steroid plus anti-VEGF plus PDT), as the preliminary work by Albert Augustin, MD, suggested that this might lead to similar results as monotherapy with anti-VEGF but with many fewer treatments. The addition of the initial intravitreal steroid at the time of the PDT therapy might reduce the initial negative effects of PDT.

RADICAL also investigated the possibility that the toxic effects of PDT could be reduced by lowering the fluence. Patients were randomized to one-quarter fluence PDT plus ranibizumab plus dexamethasone; one-half fluence PDT plus ranibizumab plus dexamethasone; one-half fluence PDT plus ranibizumab; and monotherapy with ranibizumab. Although no statistically significant differences in visual outcomes were seen between the groups (Figure 7), the group that seemed to do the best was the triple therapy group receiving one-half fluence PDT group, followed by the monotherapy group. Triple therapy seemed to reduce retreatments slightly: the ranibizumab monotherapy group had the highest number of retreatments and the triple therapy group with one-half fluence PDT had the fewest.

**Epimacular Brachytherapy.** Another option that is being
evaluated is epimacular brachytherapy, which uses a device (Vidion ANV Therapy System, Neovista, Inc.) to deliver 24 Gy of strontium 90 via a 20-gauge cannula to the retinal surface over 4 minutes after after 23- or 25-gauge pars plana vitrectomy in conjunction with anti-VEGF agents. In theory this device might permit selective treatment to the neovascularization while minimizing the collateral damage to surrounding ocular tissues.

In the nonrandomized, multicenter feasibility study that enrolled 34 patients in Mexico and Brazil predominantly classic, minimally classic or occult (with no classic) CNV, patients received a single treatment with 24 Gy beta radiation using the Vidion device and two injections of bevacizumab 1.25 mg. Group 1 received a bevacizumab injection 10 days (±4 days) prior to surgery and group 2 received an injection the time of surgery, postradiation delivery. Both groups received a second injection at 1 month postsurgery.

The mean change in visual acuity at month 18 was a gain of 6.6 letters. Seventy-three percent of patients received no additional injections, nine total additional injections were delivered by 18 months with seven patients receiving one additional injection and 1 patient receiving two.

Whether this approach is safe and efficacious as an alternative to reduce the treatment burden of monotherapy anti-VEGF agents is being investigated in a large randomized multicenter trial in the United States, CABERNET.

RETNAL VEIN OCCLUSION

In 2009, data from five large randomized trials for RVO were released.

**SCORE.** The SCORE (BRVO and CRVO) trials evaluated the standard of care for branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), laser photocoagulation (BRVO) and observation (CRVO), to a noncommercially available formulation of 4 mg triamcinolone acetonide (Trivaris, Allergan, Inc.). The BRVO trial found no significant benefit to triamcinolone over laser photocoagulation (Figure 8).\(^\text{11}\) In fact, patients treated with steroids had a significantly higher risk of cataract and glaucoma. The CRVO trial, however, demonstrated that patients may benefit from injections of triamcinolone over laser photocoagulation (Figure 9).\(^\text{12}\)

**Intravitreal Dexamethasone Implant.** The intravitreal dexamethasone implant (Ozurdex, Allergan, Inc.) trial compared the effects of the intravitreal dexamethasone implant 0.7 mg and 0.35 mg to sham in patients with BRVO and CRVO, using an endpoint of visual acuity better than or equal to 15 letters and patients were pooled together in this study. The intravitreal dexamethasone implant is currently US Food and Drug Administration (FDA)-approved for treating macular edema secondary to RVO based on the 6-month data. The duration of action of dexamethasone in this sustained-delivery vehicle is 6 months, with a peak effect occurring between 1 to 3 months.
The percentage of patients in the 0.35 mg dexamethasone group who gained equal to or better than 15 letters at 6 months was 40%; the percentage in the 0.7 mg group was 41%; and the percentage in the sham group was 23%. The mean change in best corrected visual acuity (BCVA) for patients with BRVO at the peak effect point (2 months) was 9.8 letters in the dexamethasone groups, compared to 3.1 letters in the sham group (Figure 10A). The mean change in BCVA for patients with CRVO at 2 months was 8.7 letters in the dexamethasone groups, compared to -0.5 letters in the sham group (Figure 10B).

**BRAVO and CRUISE.** In the BRAVO trial, BRVO patients were randomized 1:1:1 to 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham. Patients received monthly injections and all patients were eligible for rescue laser beginning at month 3 during the 6-month treatment period if they met the following criteria: BCVA of 20/40 or worse or mean central subfield thickness equal or greater than 250 µm. During the 6-month observation period, all patients were eligible for PRN ranibizumab (the sham group received 0.5 mg, and the 0.3 mg and 0.5 mg groups received their assigned dose) and rescue laser, if eligible.

At 6 months, the proportion of patients who gained 15 or more letters from baseline BCVA was 61.1% in the 0.5 mg ranibizumab group, 55.2% in the 0.3 mg ranibizumab group, and 28.8% in the sham group (Figure 11A). Foveal thickness was also markedly decreased in the ranibizumab groups (Figure 11B).

The CRUISE study design was essentially the same as BRAVO, except that CRUISE CRVO patients did not receive rescue laser, as previous studies have demonstrated no role for laser photocoagulation in the treatment of CRVO macular edema. During the observation period, all subjects were eligible for PRN ranibizumab treatment (the sham group received 0.5 mg ranibizumab, and the 0.3 mg and 0.5 mg groups received their assigned dose) and rescue laser, if eligible.

At 6 months, the proportion of patients who gained 15 or more letters from baseline BCVA was 61.1% in the 0.5 mg ranibizumab group, 55.2% in the 0.3 mg ranibizumab group, and 28.8% in the sham group (Figure 11A). Foveal thickness was also markedly decreased in the ranibizumab groups (Figure 11B).

**SUMMARY**

VEGF is an important pathogenic mechanism in AMD and RVO and its inhibition has been proved an effective and safe treatment for patients with these diseases. In AMD and RVO, treatments may be protracted with anti-VEGF agents or steroids. Newer agents, higher dosages, or combination therapies may offer similar outcomes with a reduced treatment burden.

These new treatments for RVO and AMD are major medical advances in the treatment of our patients. These new therapies can result in visual results that would have been unthinkably only a few years ago, and it is likely that we will look back at this past decade as one of unparalleled progress.

5. Awh CC. HORIZON extension trial of ranibizumab for neovascular AMD: first year safety and efficacy results. Paper presented at: 26th Annual Meeting of the American Society of Retina Specialists; October 11-15, 2008; Maui, HI.
Applying Current Knowledge to the Treatment of Retina Disease

BY NANCY M. HOLEKAMP, MD

EPIDEMIOLOGY AND BURDEN OF RETINA DISEASE

Age-related macular degeneration. The Eye Disease Prevalence Group has estimated that 1.75 million people in the United States have advanced age-related macular degeneration (AMD), including neovascular AMD or geographic atrophy, but not necessarily involving the foveal center, with the highest prevalence in adults older than 80 years of age. These numbers are estimated to increase substantially in the coming decades.

The numbers are huge, but what impact does AMD have on our patients? AMD is associated with an increased incidence of depression, mortality, and a greater need for assistance for daily tasks. In a quality-of-life study that was part of the Submacular Surgery Trials (SSTs), patients were asked to rate their current vision during phone interviews. Patient scores were converted to a preference value scale ranging from 1 (perfect health with perfect vision) to 0 (death). A mean preference value of 0.64 for subfoveal choroidal neovascularization (CNV) suggests a profound impact on quality of life. The impact is reported as greatest in those with the most severe loss of vision, but even patients with visual acuity of at least 20/40 in one eye had relatively low preference values. This is striking because it is right between having chronic renal failure and symptomatic HIV/AIDS (Figure 1). Clearly, AMD has a significant impact on the quality of life of individuals.

Diabetic retinopathy. It is well known that we are in the midst of an epidemic of obesity and diabetes in the United States. The rates of both have increased dramatically from 1990 to 2001, particularly in the southeast (Figure 2) and the increase in people with diabetes directly correlates to the rise in obesity. An estimated 18.2 million people had diabetes in the United States in 2002 and diabetes has been estimated to affect 151 million people worldwide, and is projected to increase to 324 million by 2025. It is also estimated that 35% of any diabetic population will have diabetic retinopathy. We know this from the Beaver Dam Eye Study. In terms of costs, the direct and indirect costs for diabetes were estimated at $312 billion in 2002. Almost $1 out of every $5 in the United States spent on healthcare is for patients with diabetes. Diabetes has an enormous impact on patients’ quality of life and represents a large economic issue.

Retinal vein occlusion. Retinal vein occlusion (RVO) is the second most common retinal disease after diabetic retinopathy. The Beaver Dam Study reported a prevalence of 0.6% in patients older than 43 years and the same study reported a 15-year cumulative incidence of BRVO of 1.8%. Although these numbers may sound low, the average age of these patients is 65 and this age group may have a host of comorbidities (eg, hypertension, vascular disease, diabetes). RVOs share risk factors with myocardial infarction (MI), stroke, and other arterial thrombotic events. In a study that is currently in press, we reviewed the records of 4,500 patients with RVO and compared them with 13,500 patients who were age-matched con-
controls. We found that patients with RVO had significantly higher likelihood of having angina, cardiac arrhythmia, congestive heart failure, diabetes, heart disease, MI or stroke, hyperlipidemia, and hypertension \( (P = .001) \) The incidence of RVOs continues to increase as the incidence of diabetes increases and the population ages.

**EVIDENCE-BASED MEDICINE**

Evidence-based medicine is the practice of medicine based on the best scientific data available. The questions are, “How much evidence do you need?” and “How much science is behind it?”

These are the various levels of evidence. The weakest is the single-case report, which is level 5 evidence. The second weakest is the case series without a comparison group (level 4). Level 3 evidence consists of nonrandomized clinical trials that may compare two groups that are not concurrent or randomized. A level 2 clinical trial is similar to a phase 2 US Food and Drug Administration (FDA) clinical trial—it is randomized and controlled but it has a high type-1 error, where a trend is apparent and may be significant, but the number of patients is insufficient. A type-2 error is when a treatment difference likely exists but, again, there are not enough patients to isolate the difference.

Level 1 evidence is from randomized, prospective, controlled trials, with a low type-1 and type-2 errors. These are the phase 3 clinical trials that eventually lead to drug approval by the FDA. The key to level 1 evidence is a well-designed study and a large number of patients.

**CLINICAL TRIAL DESIGN: WHY IS IT IMPORTANT?**

In medicine we prefer level 1 trials because of random assignment to treatment or control; the concurrent enrollment that ensures patients are being treated in a similar manner; the large numbers of patients; and the masking of the investigators. The standardized follow up is also important to the significance of outcomes. By controlling these variables, we are able to clinically treat patients in the most scientific manner. My colleague Kuldev Singh, MD, who is a glaucoma specialist has said, “This term [randomized, controlled] allows the investigator to disarm the novice scientific critic, while impugning lesser prospective and all retrospective studies, not to mention case series and reports.” The randomized, controlled study is at the top of the food chain.

A case example of using low-level evidence-based medicine upon which to base treatment decisions is that of bevacizumab (Avastin, Genentech) for treating AMD. In August 2005, there was one case report (level 5 evidence) demonstrating improvement on optical coherence tomography (OCT) for a patient nonresponsive to pegaptanib sodium (Macugen, Eyetech/Pfizer) for AMD in the published literature. Simultaneously, Philip Rosenfeld, MD, PhD, one of the authors of the aforementioned case report, presented a paper (level 4 evidence) at the American Society of Retina Specialists in Montreal on a series of patients with exudative AMD who benefited from intravitreal bevacizumab. Clearly, the “bevacizumab for AMD” era was ushered in using the least convincing type of evidence.

Unlike bevacizumab, ranibizumab (Lucentis, Genentech) was subject to two phase 3 randomized, controlled clinical trials sponsored by industry (MARINA ANCHOR) that resulted in FDA approval. The extent to which the efficacy and safety of ranibizumab has been scrutinized is to the highest level.

But can you have a randomized, controlled trial for every disease and treatment? Paul Lichter, MD, said, “Authors of case reports, retrospective studies, and other manuscripts covering the gamut of imperfect clinical projects often conclude their papers by calling for a randomized, controlled, collaborative clinical trial. While I have no idea how many times such statements are made, there is no question that these pronouncements are abundantly more frequent then the clinical trials that result from them.”

**CRITERIA FOR CONDUCTING A LEVEL 1 CLINICAL TRIAL**

Clearly, a level 1 clinical trial cannot be conducted for every clinical situation. My four criteria for conducting a randomized, controlled clinical trial include the following:

- The disease must represent a significant health problem.
- There must be scientific plausibility of benefit. In other words, there has to be some biologic basis for believing that a treatment works. An example from the AMD literature is subfoveal laser for choroidal neovascularization (CNV) in AMD. The comparison of these lasers was not a burning issue for the health care system.
- There must be scientific plausibility of benefit. In other words, there has to be some biologic basis for believing that a treatment works. An example from the AMD literature is subfoveal laser for CNV. There was no basis to suggest that applying laser to a patient’s fovea would be beneficial.
· A plausible, biologic benefit must exist. In other words, the early data on a new treatment should suggest the possibility of benefit. A good example of this is the Submacular Surgery Trials in AMD where early pilot data did not show any benefit to submacular surgery over laser photocoagulation. The eventual the long-term data supported this conclusion.

· Sufficient numbers of patients must be enrolled. If a study cannot recruit enough patients, it will not succeed. For example, it was almost impossible to recruit patients into the Macular Translocation clinical trial because they were randomized to either photodynamic therapy—a relatively painless 15-minute office-based laser procedure—or to macular translocation, which had a 25% complication rate at the time they were trying to enroll.

The clinical trials’ registry, www.clinicaltrials.gov, currently lists 530 clinical trials for the treatment of AMD. Of those 200 trials are open and actively recruiting patients. Eighty-seven of these are randomized and controlled. Those of us in the field of ophthalmology and the subspecialty of retina are fortunate to be part of a profession that is committed to providing the best scientific evidence for its members. We have a long, proud history of practicing evidence-based medicine and performing randomized clinical trials in our field.

NON-INFERIOR CLINICAL TRIALS

There are basically three types of trial design: superiority, equivalence, and non-inferiority. The Comparisons of Age-Related Macular Degeneration Treatments Trials (CATT) is a non-inferiority trial comparing intravitreal ranibizumab to intravitreal bevacizumab. The margin of non-inferiority must be pre-specified in the design protocol to construct a two-sided, 95% confidence interval (CI) to determine the true difference between the agents. To be able to declare bevacizumab noninferior, that interval must lay entirely on the positive side of the non-inferior margin.

Figure 3 helps illustrate how the results of a non-inferiority trial are interpreted. Applied to the CATT, if proved non-inferior, bevacizumab is either almost as good as, or inferior to, better than ranibizumab. If bevacizumab fails non-inferiority then it is either equivalent, almost as good as, or inferior to ranibizumab. All of those possibilities exist.

The major criteria for non-inferiority clinical trials are:
1) historical evidence that the reference drug works (ie, MARINA and ANCHOR);
2) trial design must be the same as the reference trial (ie, the CATT has same design as MARINA and ANCHOR);
3) trial conduct must be the same (ie, many of the clinical sites from MARINA and ANCHOR are also sites for the CATT);
4) the non-inferior margin (minus delta) must be acceptable (ie, six letters for the CATT).

In addition to the CATT, there are two other non-inferiority trials in AMD: HARBOR (A Study of Ranibizumab Administered Monthly or on an As-Needed Basis in Patients With Subfoveal Neovascular Age-Related Macular Degeneration) and VIEW I (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD). These are both similar to MARINA and ANCHOR in historical evidence, trial design and trial conduct, and have an acceptable non-inferior margin.

SUMMARY

The best way to practice evidence-based medicine is with phase 3, randomized, and controlled trials. The requirements for level 1 clinical trials do not necessarily constitute a “cookbook” for successful trials; rather, they provide guidelines for those who are designing and participating in clinical trials.

Finally, evidence alone is never sufficient information to make a clinical decision—there are many factors to be taken under consideration. When treating our patients, we consider several factors including a patient’s values, socio-economic status, and age; however we should rely on three main components: our years of clinical experience, the patient’s particular circumstances, and what we have learned from evidence-based medicine.
The Pathogenesis of Retinal Disease

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CME QUESTIONS

1. Inhibitors of the following might provide additional benefit if combined with VEGF-blocking agents:
   a. agents that block fibroblast growth factor
   b. agents that block ciliary neurotrophic factor
   c. agents that block platelet growth factor B
   d. all of the above

2. Inhibitors of HIF-1 (hypoxia-inducible factor 1), suppress the following:
   a. stromal derived growth factor 1
   b. vascular endothelial growth factor A
   c. platelet derived growth factor B
   d. all of the above

3. Which clinical trial is a non-inferiority trial?
   a. SCORE
   b. MARINA
   c. CATT
   d. CABERNET

4. In a quality-of-life survey from the Submacular Surgery Trials, patients rated subfoveal neovascularization as having a greater impact upon their life than:
   a. chronic liver failure requiring dialysis
   b. cataract congestive heart failure
   c. symptomatic HIV or AIDS
   d. b and c
   e. all of the above

5. A type-2 error in a clinical trial is classified as such if it has the following characteristics:
   a. a treatment difference likely exists
   b. there are not enough patients in the study to isolate the difference
   c. it is not considered a level 1 study
   d. all of the above

6. Criteria for conducting a level 1 clinical trial do not include:
   a. there must be scientific plausibility of benefit
   b. the disease must represent a significant health problem
   c. there must be a sham group
   d. none of the above

7. VEGF trap has a higher affinity binding for VEGF, thus it is hypothesized that it may have more durability than an anti-VEGF-agent.
   a. true
   b. false

8. In CRUISE, the proportion of patients who gained 15 or more letters from baseline in the 0.5 mg group was:
   a. 25%
   b. similar to the 0.3 mg group
   c. 47%
   d. b and c

9. Did you find this activity to have commercial bias?
   a. Yes
   b. No

10. Briefly describe how this activity will affect your practice patterns:
    __________________________________________________________________________________________
    __________________________________________________________________________________________
    __________________________________________________________________________________________