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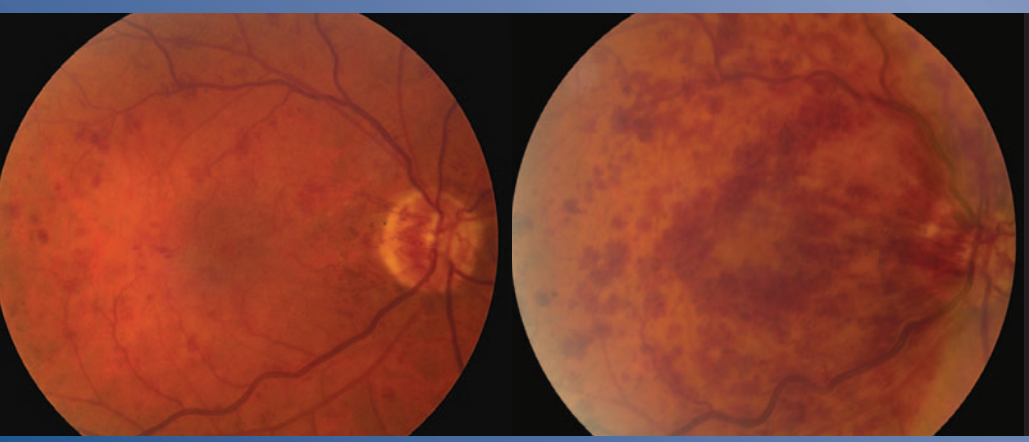
New Therapeutic Targets in the Management of Retinal Venous Occlusion (RVO)



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TARGET AUDIENCE

This activity is designed for retina specialists and other ophthalmologists.

LEARNING OBJECTIVES

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

- Describe the epidemiology and pathogenesis of central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), including the impact of systemic disease
- Understand the most frequent clinical approaches to CRVO/BRVO management
- Discuss the role of VEGF as a therapeutic target in macular edema secondary to retinal vein occlusion
- Review current and emerging clinical data evaluating the use of anti-VEGF agents for macular edema in retinal vein occlusion

METHOD OF INSTRUCTION

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Peter A. Campochiaro, MD, reports no direct financial interest in the information contained in this article; however, he reports that he has received funding from Genentech, Inc., through their physician-initiated research program and has an institutional consulting agreement with Genentech, Inc., through which Johns Hopkins University receives remuneration.

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STATEMENT OF NEED

Given the current and predicted impact of poor health in our aging society,[1-8] 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.[9-11]

Retinal vein occlusion is a common ocular disease that remains poorly understood due to the multifactorial nature of the presentation and contributing systemic factors. Several associated systemic factors have been identified and continue to be studied for their impact on retinal vein occlusion, including hypertension, diabetes, hypercholesterolemia, thyroid disorder, and ischemic heart disease. Increased intraocular pressure and axial length are other factors that play roles in this disease.[12]

In addressing the impact of systemic disease on retinal vein occlusion, it is important for ophthalmologists to discuss the current and predicted burden of disease from systemic conditions that may impact retinal vein occlusion presentation and incidence.[13] Also important is an understanding of overall health in the United States which can affect this area of retinal disease. Although the death rate from stroke and other cerebrovascular diseases has declined, it remains high for some population groups and is related to systemic hypertension. Also, although cholesterol levels have declined, the overall rate of hypertension among adults has increased from 22% in 1994 to 27% today.[3] Increasing rates of obesity, diabetes, and metabolic syndrome will have broad impact on the health care system as diseases related to these disorders increase in an aging population.[1,2,6] The association of retinal vein occlusion with several systemic diseases suggests a mounting burden on retina specialists and ophthalmologists to care for the current and future patient load presenting with retinal vascular occlusive disease.

Common current methods of clinical treatment for retinal vein occlusion include laser photocoagulation and corticosteroid injections that may not provide optimal impact on patient visual recovery following an occlusive event with subsequent macular edema.[14-16] The short and long-term visual acuity outcomes of patients undergoing these treatments continue to be discussed in relation to potential new treatment methods aimed at enhanced retinal perfusion and sustainable improvements in visual acuity.

Additionally, new treatment strategies are under study and there is emerging clinical evidence that practicing retinal specialists must consider in the management of macular edema in these patients. The use of combination treatments involving laser photocoagulation, intraocular steroid injections. and therapeutics targeting VEGF continues to be a topic of great importance among retinal specialists. As the range of available therapeutics in this area evolves, treatment patterns and timing of therapeutic intervention must be addressed by experts in the field in order to best determine effective methods of patient management.[14-20]

Also important to the effective management of these patients is the use of retinal imaging techniques to diagnose and monitor disease and therapeutic treatments. As therapeutic options advance, so does retinal imaging in providing increasing amounts of clinically relevant data and interpretive information.[21-23]

A discussion among a panel of experts to provide insight into these evolving areas of medical education related to retinal vein occlusion diagnosis, treatment, and management may provide content that will help clinicians to improve their delivery of patient care for what is likely to become an increasing public health problem.

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New Therapeutic Targets in the Management of Retinal Venous Occlusion (RVO)

INTRODUCTION

Retinal vein occlusion (RVO) is a relatively common occurrence. It is the second leading cause of blindness in patients with retinal vascular disease, following diabetic retinopathy.[1,2] In the United States, RVO is estimated to affect approximately 160,000 eyes per year, 80% of those (130,000 eyes) being branch retinal vein occlusions (BRVOs) and the remaining 20% (30,000 eyes) being central retinal vein occlusions (CRVOs). Among CRVOs, 30% (9,000 eyes) are thought to be ischemic, and 70% (21,000 eyes) are thought to be nonischemic.[1,2] These numbers illustrate the relatively high prevalence of RVO.

The demographics of RVO point more commonly to the elderly population, but we know that younger people can also present with this disease; the mean age of onset is 65 years. There are factors, such as age and vision at the time of diagnosis, that predict how patients will do with this disease, but many patients will suffer significant visual decline. We are currently at a stage that is reflective of our experiences with age-related macular degeneration (AMD) in the 2000s. We have treatment standards of care based on the Branch Vein Occlusion Study (BVOS)[3-5] and the Central Vein Occlusion Study (CVOS)[6-10] that may be considered dated by some physicians. And now, we are currently poised with greater understanding of the molecular underpinnings of the disease. Combined with our experiences with AMD and diabetic retinopathy, we have the potential to offer therapies that may have significantly better outcomes for our patients with RVO. Additionally, combination treatments also have great potential to allow physicians to approach RVO from different angles.

The timing is right to initiate discussion surrounding new treatment modalities and approaches for RVO.

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SYSTEMIC ASSOCIATIONS WITH RVO

Dr. Ho: When you see a patient with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), what kind of systemic workup do you perform, or do you refer them to an internal medicine specialist or another medical professional?

Dr. Pieramici: My approach for such a patient depends on his or her age. For patients who are older than 50 years, any associated disease will most likely be hypertension, hypercholesterolemia, glaucoma, diabetes, or other cardiovascular risk factors, so I will specifically question the patients about these conditions. Most of the time, these patients have already been diagnosed with one or more of these conditions, but it is still important to have that discussion. If a patient is not under the care of a physician for systemic conditions, I will refer them to an internist or family medical doctor with instructions to test for specific items such as blood pressure, cholesterol, or diabetes.

I also look for signs or symptoms of glaucoma in these patients, as this ocular disease is often associated with CRVO. If the patient has not had a glaucoma screening, I will refer them to a general ophthalmologist for visual field testing, particularly in the uninvolved eye.

We frequently use optical coherence tomography (OCT) imaging for both the macula and optic nerve because, although it is more time consuming for the technicians, we have found that it is helpful to evaluate the nerve fiber layer for glaucoma damage.

For patients who are younger than 50 years of age and do not have the above associated diseases, I consider the "zebra-type diseases" hypercoagulable, hyperviscosity, and inflammatory syndromes. Although these cases are rare, I refer these patients to a hematologist as well as their general physician for further testing.

Finally, patients who present with bilateral simultaneous vein occlusion require more thorough testing and I refer all of these patients to an internist or hematologist.

Dr. Ho: Dr. Campochiaro, how is your management or workup similar or dissimilar from Dr. Pieramici's when dilating a new patient who presents with BRVO or CRVO?

Dr. Campochiaro: My workup is similar. For these patients, it is important to focus on hypertension. Other factors, such as hypercholesterolemia, glaucoma, or diabetes, may enhance the risk to a degree, but poorly controlled hypertension can have a major impact and its treatment can provide benefit. In the past, I have obtained homocystine levels, but I have found that they are rarely elevated. Currently, I will perform tests like serum protein electrophoresis or homocystine levels only in a few select cases where other symptoms point to a systemic condition or bilateral disease.

Dr. Ho: When would you initiate a hematology consult for ruling out hypercoagulable states when the case is not a bilateral retinal vein occlusion?

Dr. Campochiaro: If, when taking the patient's history, there is bone pain, weight loss, or other concerning symptoms that suggest malignancy, particularly multiple myeloma, or a clotting abnormality.

Dr. Pieramici: I agree. Younger patients tend to worry me because they do not usually have the concomitant systemic diseases, such as hypertension, that are typical with RVO. However, in my experience, the workup in these younger patients is still most often negative.

PATHOGENESIS AND PRESENTATION OF RVO

Dr. Ho: What is our current understanding of the pathogenesis of BRVO, and mechanisms that lead to vision loss from that?

Dr. Campochiaro: There is fairly strong evidence that hypertension is a major systemic risk factor for BRVO.[11,12] The theory is that chronic hypertension causes a thickening of the arterial wall. In areas where the arterioles cross over venules, the thickened arteriolar wall can create more pressure on the venule and alter flow which causes damage to the endothelium. This makes the luminal surface more thrombogenic, causing clot formation and occlusion of the vein. Frequently, we can see evidence of thickened arterioles in fundus images from patients with BRVO.

Dr. Ho: What about CRVO?

Dr. Brown: Our current understanding of CRVO is that it stems from a blockage of the main vein draining the eye.[13] This central retinal vein travels posteriorly from the optic nerve head, where it occasionally bifurcates with collateral vessels all draining venous blood from the eye. A thrombus or an occlusion of the central retinal vein that occurs anterior to the collateral formations inhibits all the drainage. If the venous pressure rises higher than arterial pressure, perfusion no longer exists in the eye, resulting in ischemic CRVO. In nonischemic CRVO, the occlusion theoretically occurs further back in the optic nerve where the venous drainage from the collaterals are adequate to maintain venous pressure below arterial pressure.

The pathophysiology of vein occlusions is mechanical. For example, if a leg vein becomes occluded, bruising and swelling will occur in the lower extremity, where the vein

drains. I originally thought that the edema in vein occlusion was at least in part due to the increased pressure in the venous circulation, but we found out that when we treat these eyes with antivascular endothelial growth factor (anti-VEGF) agent most of the edema dissipates, suggesting that it is primarily ischemia-mediated. The hemorrhaging seems to be self-limited but the retinal edema resolves quickly in some patients and does not resolve at all in others.

Dr. Ho: What is a classic clinical presentation of BRVO?

Dr. Avery: The typical finding in BRVO is scattered intraretinal hemorrhage in the distribution of a retinal vein distal to a blockage site which occurs at the crossing of a retinal artery. Occasionally, cotton wool spots are apparent on fundus imaging, and retinal edema frequently spreads into the macula in symptomatic BRVOs which most commonly occur in the superior-temporal quadrant.

In the later stages, patients may develop neovascularization due to the areas of nonperfusion and VEGF elaboration, and in very severe cases, subsequently progress to vitreous hemorrhage and/or tractional detachment.

Dr. Ho: How do patients with CRVO typically present?

Dr. Pieramici: On fundus examination and imaging, a significant amount of hemorrhage is often present in all quadrants of the retina. We may also find macular edema and/or cotton wool spots, and in some cases, vitreous hemorrhage. Swelling of the optic nerve is a common finding and in some cases may be out of proportion to the hemorrhages seen in the retina. Dilation and tortuosity of the retinal veins is present early on and with the development of collateral vessels or recannulation of the retinal vein may resolve.

An ischemic CRVO may present with neovascularization of the iris or neovascular glaucoma in more severe cases. A perfused or nonischemic CRVO, while having similar fundus findings as the ischemic, albeit to a lesser extent, does not develop neovascularization of the iris or neovascular glaucoma. Retinal neovascularization is very uncommon in cases of CRVO even in ischemic patients with vitreous hemorrhage. Vision loss in patients with CRVO is primarily associated with the development of macular edema, but in many of the ischemic cases, inner retinal ischemia damage plays a major part in the reduced vision.

Dr. Ho: What is your diagnostic workup for patients with RVO?

Dr. Brown: I tell my patients who present with CRVO that there are four main risk factors: diabetes, hypertension, older age, and bad luck. After a laugh, most people realize that they have at least two and some have three and four. If bad luck appears to be the only risk factor a patient has, I check the patient's hemoglobin A1C levels and/or do a spot glucose test; I also will test patients intermittently for hypertension because this is the most significant risk for patients with RVO. If the patient is younger than 45 or 50 years of age and has multiple occlusions, we typically look for clotting disorders of a hypercoagulable nature.

Upon presentation, we perform the clinical exam, using gonioscopy to look for the possibility of neovascularization or rubeosis in the anterior segment. We also use OCT to monitor their macular thickness and fluorescein angiography to assess perfusion. Using wide-field angiography, we obtain a 135° view, which is helpful in detecting ischemia. For patients who are significantly hemorrhagic, however, the obstructed view can cause a misleading fluorescein. For patients who are one-eyed or for whom temporarily decreased vision would be a significant impairment, we will offer immediate intervention. For most patients, however, we explain that RVO is a fairly acute event, and that many of these patients get better on their own and that our choice of management is to follow them with clinical and diagnostic testing.

Dr. Campochiaro: I generally use OCT and fluorescein angiography for baseline measurements and follow-up primarily with OCT, but occasionally get follow up angiograms when indicated to assess capillary nonperfusion.

RATIONALE FOR ANTI-VEGF THERAPY IN RVO

Dr. Ho: The BVOS showed some benefit for treatment with laser. For example, 20% of those patients treated with macular grid laser gained two lines of vision at 1 year vs only 7% of patients in the observation group.[3] At 3 years, there was a mean visual acuity gain of at 3 years of 6.7 letters in the laser group vs only 1 letter in the observation group. So, clearly there are benefits to laser treatment.

The protocol in BVOS was to wait for 3 months before any intervention (laser) was initiated due to the 30% chance of spontaneous recovery.[3] There was a 70% chance that the macular edema would not regress or that it may even worsen, and now that we have a potential treatment in anti-VEGF agents, such as ranibizumab (Lucentis, Genentech) or bevacizumab (Avastin, Genentech), a 3-month wait for our patients who may not improve is no longer necessary. Because there is not a US Food and Drug Administration-approved indication for an anti-VEGF for RVO, however, an unmet need continues to exist for our patients.

Currently, when do you intervene with treatment for patients with RVO?

Dr. Campochiaro: When laser was our most frequently

TABLE 1. OCULAR SERIOUS ADVERSE EVENTS						
	MARINA + ANCHOR (COMBINED)					
	Year 1 (final study database)			Year 2 - Cumulative		
		Ranibizumab			Ranibizumab	
	Control * (n=379)	0.3 mg (n=375)	0.5 mg (n=379)	Control * (n=379)	0.3 mg (n=375)	0.5 mg (n=379)
Presumed Endophthalmitis†						
• Culture positive	0	0	1 (0.3%)	0	0	1 (0.3%)
• Culture negative	0	0	2 (0.5%) ‡	0	1 (0.3%)	4 (1.1%) ‡
• Culture not done	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%) §
Uveitis	0	2 (0.5%)	2 (0.5%)	0	3 (0.8%)	4 (1.1%)§**
Rheg. retinal detachment	1 (0.3%)††	1 (0.3%)††	0	2 (0.5%)††	2 (0.5%)	0
Retinal tear	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	2 (0.5%)
Vitreous hemorrhage	0	2 (0.5%)	1 (0.3%)	2 (0.5%)	3 (0.8%)	1 (0.3%)
Lens damage	0	0	1 (0.3%)	0	0	1 (0.3%)

** Sham injection-control for MARINA and active treatment-control with verteporfin PDT for ANCHOR*

† Defined as cases reported of endophthalmitis or uveitis in which intravitreal or systemic antibiotics were administered

‡ One case was reported as uveitis

§ One patient was reported as having 2 episodes of uveitis in 1st treatment year and was treated with systemic antibiotics for the 1st episode. A vitreous culture was not done.

*** One patient had two episodes of uveitis and was discontinued after the 2nd episode*

†† One patient had 2 episodes

CVA=cerebrovascular accident (including stroke)

CHF=congestive heart failure

NHL=non-Hodgkin's lymphoma

CAD=coronary artery disease

used intervention for RVO, we were forced to wait until severe macular hemorrhages reabsorbed before doing laser. Having anti-VEGF agents allows us to treat every patient early regardless of the presence of hemorrhage. We can then determine later if an alteration in treatment course is necessary.

Dr. Avery: I agree. The indications for intervention in my practice have changed due to my use of anti-VEGF agents. Back when all we had was laser, we only considered patients with BRVO and 20/40 or worse vision candidates for treatment. Even then, we may have waited 3 months before intervening, and certainly we would wait for the blood to clear in cases where there was significant intraretinal hemorrhage. We now have the ability to combat the edema much earlier.

I now wrestle with whether I am intervening too soon in some cases. Given the natural course of spontaneous resolution in many of these patients, should I still wait until I see some progression? I will often observe a patient for one visit, even in the presence of mild edema, and bring them back in a short period of time to see if the edema is regressing or progressing before I offer an anti-VEGF injection. Although I do not want to commit patients who may eventually have spontaneous resolution to frequent injections, retinal edema is probably not a good condition for the long term. Now that we have the ability to treat edema effectively with anti-VEGF agents regardless of the status of the blood in the retina, we can achieve a better visual outcome and minimize the exposure of the fovea to cystic edema.

Dr. Pieramici: I have definitely moved toward earlier treatment in RVO. Based on the low systemic and ocular risk profile of anti-VEGF agents that we have witnessed for the treatment of AMD (see Tables 1 and 2), I am comfortable using these agents to treat macular edema associated with RVO. In addition to reducing macular edema, it also seems that we can improve other parameters, such as reducing intraretinal hemorrhage, venous caliber, optic nerve swelling, and in some cases, it has been suggested that anti-VEGF agents have a positive effect on the thrombosis itself. So, I tend to treat patients earlier with anti-VEGF agents either in conjunction with laser for BRVO patients or prior to laser when significant hemorrhage precludes laser treatment. The CRVO patient can be treated at the time of presentation or following a short period of observation. For patients who are hesitant, however, I will provide them with information concerning the anti-VEGF agents and follow-up with them in 4 or 5 weeks.

Dr. Ho: What is our current evidence for the role of VEGF in retinal vein occlusion, and therefore anti-VEGF as a targeted therapy?

Dr. Brown: There is good evidence from both preclinical and histopathologic studies that suggest VEGF plays an important role in RVO. Aiello et al[14] found that VEGF levels are higher in the ocular fluid of patients with venous occlusive disease than other disease states studied. Boyd et al[15] also found that there was a correlation between increased levels of VEGF and perfusion in CRVO. Additionally, Pe'er et al[16] found upregulation of VEGF mRNA in enucleated eyes with proliferative diabetic retinopathy and neovascular glaucoma.

Dr. Campochiaro: One of our observations made after hemorrhages have reabsorbed is that there is frequently capillary nonperfusion; from our experience with diabetic retinopathy and other ischemic retinopathies we know that capillary nonperfusion results in upregulation of VEGF contributing to leakage and neovascularization. Vascular leakage in patients with RVO is due not only to increased in venous pressure from the occlusion, but also to reduced perfusion that leads to capillary dropout. The capillary dropout is the long-term problem: the blockage itself may be ameliorated but areas of capillary nonperfusion remain. We have learned that this process begins much earlier than we previously thought and that blocking VEGF at these earlier stages may help to improve outcomes.[17]

Dr. Avery: Neovascularization is a long-term sequela of the nonperfusion, so when devising long-term treatment plans, we must understand how VEGF mediates both edema and neovascularization. For example, will we continue to administer anti-VEGF agents, or will we use laser in combination to treat these areas of nonperfusion in order to decrease VEGF and to reduce edema and the neovascular drive? One of our unmet goals in treating patients with RVO is to determine how best to combine photocoagulation with anti-VEGF therapies.

MANAGEMENT STRATEGIES FOR RVO

Dr. Ho: Let's take the scenario of a patient with newly diagnosed BRVO, 20/80 vision, moderate hemorrhage, superotemporal BRVO, macular edema, and no neovascularization. The onset of the vision loss was 4 weeks prior. How would the panel manage this patient?

Dr. Pieramici: For a patient with BRVO and the signs that you describe, I may be less aggressive with anti-VEGF therapy; however, I would not rule out this strategy. Most commonly, I initially discuss the options, including photocoagulation, and send the patient home with information. Assuming I find no neovascularization or other conditions that would require a more urgent approach, I will

TABLE 2. KEY SYSTEMIC SAFETY FINDINGS POTENTIALLY RELATED TO VEGF-A INHIBITION

	MARINA + ANCHOR (Combined)					
	Year 1 (final study database)			Year 2 - Cumulative		
		Ranibizumab			Ranibizumab	
	Control (n=379)	0.3 mg (n=375)	0.5 mg (n=379)	Control (n=379)	0.3 mg (n=375)	0.5 mg (n=379)
Deaths						
• Nonvascular	1 (0.3%)	2 (0.5%)	1 (0.3%)	4 (1.1%)	5 (1.3%)	4 (1.1%)
• Vascular*	1 (0.3%)	2 (0.5%)	3 (0.8%)	7 (1.8%)	5 (1.3%)	5 (1.3%)
Nonfatal MI*	2 (0.5%)	3 (0.8%)	4 (1.1%)	6 (1.6%)	7 (1.9%)	8 (2.1%)
Nonfatal CVA*	2 (0.5%)	2 (0.5%)	3 (0.8%)	4 (1.1%)	6 (1.6%)	6 (1.6%)
Hypertension	38 (10.0%)	24 (6.4%)	34 (9.0%)	61 (16.1%)	54 (14.4%)	56 (14.8%)
Mean change in SBP/DBP (mmHg) at month 12/24†	-1/1	-1/2	-4/0	-4/-3	-2/-2	-4/-1
Proteinuria	0	0	0	1 (0.3%)	0	0
Nonocular hemorrhage‡	13 (3.4%)	16 (4.3%)	13 (3.4%)	20 (5.3%)	34 (9.1%)	34 (9.0%)

** Antiplatelet Trialists' Collaboration (APTC) Arterial Thromboembolic Events. Antiplatelet Trialists Collaboration, BMJ. 1994308(6921):81 used during FDA COX-2 inhibitor advisory panel meetings February 2005*

† N's vary because not all patients had their blood pressure taken at 12 and 24 months

‡ Includes epistaxis, hematuria, ecchymosis, hematoma, GI hemorrhage, subdural hematoma, duodenal ulcer hemorrhage, hematemesis, subarachnoid hemorrhage, etc

CVA=cerebrovascular accident (including stroke)

CHF=congestive heart failure

NHL=Non-Hodgkin's lymphoma

CAD=coronary artery disease

see the patient back in 3 to 4 weeks, repeat the OCT, and if the hemorrhage has cleared but the edema is still present or has worsened, I would consider focal laser treatment as a more traditional approach. If the patient is comfortable with a newer off-label approach, I will consider using an anti-VEGF agent, possibly in conjunction with laser at the same visit.

Dr. Brown: Much of my decision in treating this patient depends on the vein occlusion and the patient. In general, I am in agreement with Dr. Pieramici; however, there have been many times in retina history that we have jumped over a gold standard to a new therapy only to find that, after the randomized clinical trial results are available, the tried-and-true tested response may be the better one. The interesting thing about our treatment for BRVO is that we have not had a major advance proven by clinical trial since 1976. Finally, in 2009 we expect to have the results of three large clinical trials: SCORE (Standard Care vs. COrticosteroid for REtinal Vein Occlusion), BRAVO (A phase 3, multicenter, randomized, sham injection-controlled study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema secondary to BRVO), and CRUISE (A phase 3, multicenter, randomized, sham injection-controlled study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema secondary to CRVO). The first tests steroids against laser, and the latter two trials test ranibizumab against laser.

For this patient, I would wait 1 month to see if he improved, and in the meantime have him tested for hypertension and diabetes if he is not already diagnosed with either of these conditions. Upon his return in 1 month, if the patient's condition is declining, I will typically offer grid laser per the BVOS guidelines, although I will tell him that this treatment will often result in slow improvement. If the patient has a job that requires binoclar vision, however, I will probably make a strong recommendation for anti-VEGF therapy to enable faster improvement.

Dr. Avery: I might be more aggressive than either Dr. Pieramici or Dr. Brown if the patient has moderate intraretinal hemorrhage and known visual loss for 1 month. For this situation, I will most likely lean toward anti-VEGF therapy because I believe that it speeds the rate at which intraretinal hemorrhages resolve. My typical plan is to minimize the edema as rapidly as possible, and this most often relies on an anti-VEGF agent. Laser factors into my treatment plan eventually. Once I have cleared the hemorrhage, hopefully, I can minimize the length of time that the fovea is edematous and have a better visual outcome after laser. Until we have evidence on anti-VEGF agents for RVO, however, the information that I have on the mechanism of action of anti-VEGF agents and the pathogenesis of BRVO and CRVO is currently based solely on anecdotal experience.

As Dr. Pieramici mentioned, it is important to offer patients the gold standard of laser but this is not even an option if one is following the BVOS guidelines and waiting the recommended 3 months. Even if I were not following the guidelines and waiting, this patient would not even be able to have laser because of the moderate hemorrhaging.

Dr. Ho: Would you give the patient an anti-VEGF injection on day 1?

Dr. Avery: Most likely, especially if I know that visual acuity has been poor for at least 1 month.

Dr. Campochiaro: Many patients with BRVO present fairly soon after onset of the occlusion when the macula is involved and they often have severe hemorrhages in the macula. In such patients, laser is not an option because it can damage the inner retina when hemorrhages are present. Although we are still awaiting data from the BRAVO and CRUISE studies, we do have a fairly good understanding of how anti-VEGF agents work in patients with macular edema due to RVO. As was previously mentioned, some patients' edema may resolve spontaneously over time, but reducing edema is never a bad thing and the risks of treatment with anti-VEGF agents are so low, that early treatment may be considered. A patient who receives injections for severe edema at an early stage of disease is not committed to frequent injections and there are potential benefits from reducing edema at an early stage even if it might resolve spontaneously several months down the road, because their ultimate outcome may be improved and at the very least the duration of visual disability is likely to be reduced. Often we see retinal thicknesses of 600 µm to 700 µm along with massive cysts in many of these patients. I believe that the data will confirm a correlation between the presence of long-term edema and poor visual outcomes. Currently, I tend to enroll these patients in clinical trials, but I have no objection to the idea of treating a patient on day 1 with an anti-VEGF agent if they present a month out with severe edema and hemorrhaging.

Dr. Ho: Consider a patient who presents 14 months after an initial event where the hemorrhaging has resolved, but the edema persists and visual acuity is 20/200. Would anyone not consider treatment for this patient?

Dr. Campochiaro: I think we are all in agreement that long-term edema is not a good thing. In BRAVO and CRUISE, however, one thing that surprised me was that

CENTRAL VEIN OCCLUSION STUDY (CVOS)*

PURPOSE

1. To determine whether photocoagulation therapy can help prevent iris neovascularization in eyes with central retinal vein occlusion (CRVO) and evidence of ischemic retina.

2. To assess whether grid-pattern photocoagulation therapy will reduce loss of central visual acuity due to macular edema secondary to CRVO.

3. To develop new data describing the course and prognosis for eyes with CRVO.

DESCRIPTION

Eligible patients were divided into four groups:

Group M—Eyes with visual loss ascribable to macular edema were randomly assigned to receive grid-pattern photocoagulation or nontreatment.

Group N—Eyes with extensive retinal ischemia (at least 10 disc areas of nonperfusion) were randomly assigned to receive panretinal photocoagulation (PRP) or nontreatment unless iris neovascularization developed.

Group P—Eyes with relatively perfused retinas were followed to provide information about the natural history of the disease.

Group I—Indeterminate eyes in which the retina could not be visualized accurately because of hemorrhage were followed in a natural history study.

Green argon laser with a slit lamp delivery system was used for all treatments.

EVALUATION METHODS

Photographic documentation of retinal changes was obtained at entry, posttreatment, and at specified follow-up visits for a period of at least 3 years. The frequency of follow-up visits varied according to the group to which the CRVO patient was assigned. Visual acuity, the primary outcome factor in the group with macular edema, was measured according to a modified Early Treatment Diabetic Retinopathy Study protocol at each visit.

PATIENT ELIGIBILITY

To be eligible, patients had to be 21 or older and willing to return for follow-up visits for 3 years following assignment into the appropriate group and randomization. Each of the four groups has specific eligibility criteria. Patients with retinal vascular disease other than that specified in the criteria, such as diabetic retinopathy, were ineligible. Patients with macular disease other than that due to CVO were ineligible for that portion of the study.

Recruitment began in August 1988 and ended in July 1992. Follow-up was completed in February 1994.

RESULTS

Group M—Macular Edema: Macular grid photocoagulation was effective in reducing angiographic evidence of macular edema but did not improve visual acuity in eyes with reduced vision due to macular edema from CRVO.

Group N—PRP for nonischemic CRVO: Prophylactic PRP did not prevent the development of iris neovascularization in eyes with 10 or more disc areas of retinal capillary nonperfusion confirmed by fluorescein angiography. Rather, results of this randomized clinical trial demonstrate that it is safe to wait for the development of early iris neovascularization and then apply PRP.

Group I—Indeterminate: Eyes with such extensive intraretinal hemorrhage that it is not possible to determine the retinal capillary perfusion status act as if they are ischemic or nonperfused.

PUBLICATIONS

The Central Vein Occlusion Study Group: Natural history and clinical management of central retinal vein occlusion. *Arch Ophthalmol.* 1997;115:486–491.

The Central Vein Occlusion Study Group: Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The CVOS Group M Report. *Ophthalmology.* 1995;102:1425–1433.

The Central Vein Occlusion Study Group: A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The CVOS Group N Report. *Ophthalmology.* 1995;102:1434–1444.

Clarkson JG, Central Vein Occlusion Study Group: Central vein occlusion study: Photographic protocol and early natural history. *Trans Am Ophthalmol Soc.* 1994;92:203–215.

The Central Vein Occlusion Study Group: Baseline and early natural history report. *Arch Ophthalmol.* 1993;111:1087–1095.

**Information from National Eye Institute's Clinical Studies Database. Available at: http://www.nei.nih.gov/neitrials/viewStudyWeb.aspx?id=30. Accessed May 20, 2009.*

BRANCH VEIN OCCLUSION STUDY*

PURPOSE

1. To determine whether scatter argon laser photocoagulation can prevent the development of neovascularization.

2. To determine whether peripheral scatter argon laser photocoagulation can prevent vitreous hemorrhage.

3. To determine whether macular argon laser photocoagulation can improve visual acuity in eyes with macular edema reducing vision to 20/40 or worse.

DESCRIPTION

Approximately 500 patients were enrolled in the study and divided equally among two groups.

Group 1—One half of patients were randomized to treatment: For branch retinal vein occlusion (BRVO) with or without neovascularization, scatter treatment of 100 to 400 laser burns was applied in the drainage area of the occluded vein site, avoiding the fovea and optic disc. Individual laser burns were 200 µm to 500 µm in diameter with an exposure time of 0.1 to 0.2 seconds.

For macular edema, burns of 50 µm to 100 µm in diameter with exposure time of 0.05 to 0.1 seconds were used.

Group 2—Control (no treatment).

EVALUATION METHODS

A fluorescein angiogram less than 1 month old was necessary for all patients. Treatment was performed under topical anesthesia using the argon laser to achieve a grid pattern over the area of capillary leakage identified by fluorescein in the macular region. Photocoagulation was extended no closer to the fovea than the edge of the foveal avascular zone and did not extend peripherally beyond the major vascular arcade. The efficacy of treatment was judged on the basis of visual acuity measurements as well as assessment of the subsequent development of neovascularization and/or vitreous hemorrhage. Patients were followed for at least 3 years.

PATIENT ELIGIBILITY

Patients with three types of diagnoses were accepted:

1. Major BRVO without neovascularization
2. Major BRVO with neovascularization
3. BRVO with macular edema and reduced vision

All patients must have had onset of signs and/or symptoms of BRVO less than 18 months before the initial visit, vision of 5/200 or better, and sufficient clarity of the ocular media to permit confirmation of the condition with fundus photography. Other eligibility criteria apply to each of the three major groups as well as special cases such as the occurrence of bilateral disease.

Patient recruitment began in July 1977 and ended in February 1985.

RESULTS

Results from this 8-year study indicated that use of argon laser photocoagulation can benefit those afflicted with certain types of BRVO. The results indicated that argon laser treatment improves sight significantly in patients who already have reduced vision due to macular edema secondary to BRVO. Laser appeared to significantly reduce the likelihood of vitreous hemorrhage.

PUBLICATIONS

Branch Vein Occlusion Study Group: Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion. *Arch Ophthalmol.* 1986;104:34–41.

Branch Vein Occlusion Study Group: Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol.* 1984;98:271–282.

**Information from National Eye Institute's Clinical Studies Database. Available at: http://www.nei.nih.gov/neitrials/viewStudyWeb.aspx?id=64. Accessed May 20, 2009.*

many patients who had chronic edema for several years experienced improvement after treatment with anti-VEGF agents. Based on this information, I am not likely to give up on a patient who has chronic edema until they have an adequate trial with anti-VEGF agents to see if the vision can improve.

Dr. Pieramici: I agree. We have had many patients who had chronic edema for 6 months to 1 year and we had good outcomes with anti-VEGF agents. Our prospective and retrospective data using anti-VEGF agents indicates that significant visual improvement may occur by reducing the macular edema even a year after its onset.

Dr. Brown: In order to improve visual acuity with anti-VEGF agents, in my experience, the anatomy with chronic edema in diabetic macular edema (DME), CRVO, or BRVO must be VEGF-responsive; visual acuity gain with very thin central foveal thickness (80 µm to 100 µm) is possible, proving that you do not need to have all of the retina to achieve good results. If there is

no anatomic improvement, however, I do not think the patient will improve with anti-VEGF agents.

Dr. Avery: In my experience, RVO-related edema is much more responsive to anti-VEGF agents than DME. Even pegaptanib sodium (Macugen, Eyetech/Pfizer), which is an anti-VEGF agent that is weaker than ranibizumab or bevacizumab, seems to work well for patients with RVO. My experience with bevacizumab for vein occlusion has been that for patients with chronic cystoid macular edema that has caused extensive macular atrophy, there is nice flattening of the retina, but no visual acuity improvement. Upon examination with spectral-domain OCT, it is apparent that these patients have often lost their outer retina and that the cumulative damage from long-term CME is irreversible to some extent.

For DME, I have had little success with bevacizumab, except for patients who have concurrent rubeosis. If there is enough VEGF present to produce rubeosis, you probably have enough floating around to induce VEGF-responsive macular edema. My clinical experience is that eyes with ischemia and edema from diabetes seem to respond to anti-VEGF more than the eyes with early DME with only a little lipid and a few microaneurysms but not a significant amount of ischemia. This lack of response may be due to a secondary or different mechanism.

Dr. Ho: It is clear that macular edema is multifactorial in its etiology, particularly in patients with diabetes. We had seen that early on the response of the macular edema to anti-VEGF agents has been more variable than in patients with AMD. For patients with RVO, however, I find that most respond well to anti-VEGF agents. So my impression is that the edema in the vein occlusion patient is much more mediated by VEGF, whereas in the diabetic patient, there are some cases that are VEGF-mediated and some cases in which the edema is the result of some other mechanism. Do others on this panel agree?

Dr. Brown: I agree. A patient with diabetes is less likely to have a posterior vitreous detachment, so if a significant amount of edema exists and if an anti-VEGF agent is employed, vitreomacular traction may result. The majority of vein occlusions, however, respond well to anti-VEGF agents.

Dr. Campochiaro: I agree that patients with DME seem to be the most difficult to treat. We have found that aqueous VEGF levels are highest in patients with DME. In patients with macular edema due to RVO, there was an inverse correlation between aqueous VEGF level at baseline and visual outcome. Because patients with DME tend to have high intraocular levels of VEGF, this is likely to be one factor that makes them more difficult to treat. It is my impression that ranibizumab may be superior to bevacizumab for DME, but not for patients with neovascular AMD. Vein occlusions may fall in between. These are just impressions, but it is interesting to speculate as to what would explain them if they are correct. The different levels of VEGF in the different disease processes could play a role, but there also may be differences in treating retinal versus choroidal diseases.

Dr. Avery: Have you found that your results with RVO correlated VEGF levels intravitreally to the amount of nonperfusion or the thickness of the macular edema in BRVO?

Dr. Campochiaro: I have not. I do not have a wide-angle camera, so I have not made a rigorous study of such a correlation. I do think that it would certainly make sense that the VEGF level should correlate to the amount of nonperfusion.

FUTURE OF THERAPY FOR RVO

Dr. Ho: We are currently looking forward to the imminent results of the Posurdex steroid implant trial, SCORE trial, and also the BRAVO and CRUISE trials. Dr. Brown, what do you think that can we expect from the results of SCORE?

Dr. Brown: When corticosteroids were first used in retinal disease, many of us were nearly certain that these were the answer that we had been seeking and as such, were injecting steroids for just about anything. The results of the DRCR Protocol B study[18] showed that the benefits to steroids for treating DME may be short-lived, and that the side effects may make them inferior to the standard of care. The 2- and 3-year data for steroids in RVO are highly anticipated. Anecdotally, steroids do seem to have a positive effect on macular edema associated with BRVO and CRVO, but the real questions that we hope to gain answers to in this study are whether the side effects of steroids are acceptable and whether there is a drop off in efficacy for RVO as was seen in DME. At the end of the day, is natural history or laser better than steroids?

The next step is to test ranibizumab vs laser. This is being evaluated in the BRAVO and CRUISE trials. Many anti-VEGF agents are clinically effective immediately and do not have the side effects of glaucoma and cataract that we see with steroids, so many retinal specialists are under the impression that anti-VEGF will be found to be superior to laser. The results of both BRAVO and CRUISE will be presented at the 2009 combined Retina Congress.

Dr. Ho: Where would you predict us to be in 2 to 5 years in regard to treatment of RVO?

Dr. Pieramici: Much of this will depend on the data from SCORE, BRAVO, and CRUISE. What these data will not tell us, however, is how combination treatment with laser, anti-VEGF agent, and steroid will work. It is my gut feeling that our experience with RVO will mirror AMD—where there is a clear-cut benefit to anti-VEGF agents for RVO, but that, after many months of using monotherapy, we will be looking for longer-lasting treatments and ways to extend delivery because many of our patients will require frequent injections over a long period of time.

Dr. Campochiaro: It is likely that in BRVO, early treatment will be performed with anti-VEGF agents, and if a moderate number of injections achieves sustained resolution of edema and visual improvement, the treatment will be considered successful. If it turns out that a patient is requiring frequent injections after macular hemorrhages have cleared, then grid laser treatment can be done. I foresee a similar scenario with CRVO and anti-VEGF agents, but there may be more of a role for sustained delivery of steroids for this indication. We know from the Central Retinal Vein Occlusion Study that laser alone is not effective, but I would not rule it out as adjunctive therapy for CRVO. Currently, there is still little data to guide us in the long-term management of capillary nonperfusion that requires frequent injections of anti-VEGF agents to prevent recurrence of macular edema and maintain visual benefits.

Dr. Brown: I agree that immediately, short-term use of anti-VEGF agents will be the answer for RVO in many cases. There are many patients, however, for whom long-term therapy with anti-VEGF agents will be necessary and for these, we might find ourselves turning to cheaper off-label anti-VEGF agents to manage the macular edema.

I have always been under the impression that in an ischemic event, parts of the retina die and others would survive, decreasing the impetus for VEGF production. What seems to be happening in many patients, is that the some of the damaged cells never really die but continue to secrete VEGF. If we can identify which cells are secreting the anti-VEGF, and either make those healthier or kill them off, we could turn off the spigot, and get rid of the "sponge" of anti-VEGF that we are throwing in to mitigate excess VEGF. I am hopeful that in 3 to 5 years, we will have the ability to determine which cells are secreting VEGF and find a way to turn it off at the source.

Dr. Avery: I also agree that we will be using anti-VEGF agents in the early periods of disease presentation and for the patients who continue to require treatment we will supplement therapy with laser to reduce the frequency of injections for BRVO, and to a greater extent, CRVO.

I have read with interest reports of surgery to create intraoperative anastomoses with the choroid and increased oxygenation of vitrectomy.[19] Although it is difficult to provide comment on such novel procedures, these reports remind us that surgical intervention is another area that may provide promise in the future. I also think we have to pay attention to collateral vessel formation and whether anti-VEGF will show any harmful effects to these.

Dr. Ho: Anti-VEGF therapy has great promise as a future cornerstone in BRVO and CRVO, perhaps in combination with other therapies such as corticosteroids or laser. Ranibizumab is known to be safe for up to 4 years in the combined studies for AMD and so our level of comfort with this agent is relatively high. With anti-VEGF agents, there is the potential to treat our RVO patients earlier and possibly improve final visual outcomes. We look forward to data from large clinical trials to guide us in our future treatment decisions for RVO.

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NEW THERAPEUTIC TARGETS IN THE MANAGEMENT OF RETINAL VENOUS OCCLUSION (RVO)
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CME QUESTIONS

1. Retinal venous occlusive diseases are associated with which systemic conditions?

a. hypertension and glaucoma
b. diabetes
c. hypercholesterolemia
d. all of the above

2. A frequent fundus image finding in patients with BRVO is:

a. arteriole thickening
b. cotton wool spots
c. A and B
d. none of the above

3. Iris neovascularization and neovascular glaucoma are likely to present with:

a. perfused eyes
b. ischemic CRVO
c. nonischemic CRVO with hemorrhaging
d. all of the above

4. The BVOS showed a benefit to laser treatment for BRVO in that:

a. 20% of patients treated with laser gained five lines of vision in the first year
b. 7% of patients in the observation group lost two lines of vision in the first year
c. 20% of patients treated with laser gained two lines of vision in the first year
d. 7% of patients in the observation group gained one line of vision in the first year.

5. The protocol in BVOS was to wait for ___ months prior to laser treatment because of a ___ % chance of spontaneous recovery:

a. 2/50%
b. 3/30%
c. 3/50%
d. 2/30%

6. VEGF levels have been shown to be higher in RVO than AMD :

a. True
b. False

7. In the CVOS, PRP was shown to:

a. have no prophylactic effect against iris neovascularization in eyes with 10 or more disc areas of retinal capillary nonperfusion
b. be effective when used to treat early iris neovascularization
c. have no effect on iris neovascualrization
d. A and B

8. In the DRCR.net Protocol B study, steroids were shown to:

a. be significantly ineffective vs laser for DME
b. not as effective as laser in the long term for DME
c. have a short-lived period of efficacy against DME
d. B and C

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NEW THERAPEUTIC TARGETS IN THE MANAGEMENT OF RETINAL VENOUS OCCLUSION (RVO)
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Would you recommend this program to a colleague? ❒ Yes ❒ No

Do you feel the information presented will change your patient care? ❒ Yes ❒ No
If yes, please specify. We will contact you by e-mail in 2 to 3 months to see if you have made this change.

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If no, please identify barriers to change.

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List any additional topics you would like to see offered at future Dulaney Foundation programs or other suggestions or comments.

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