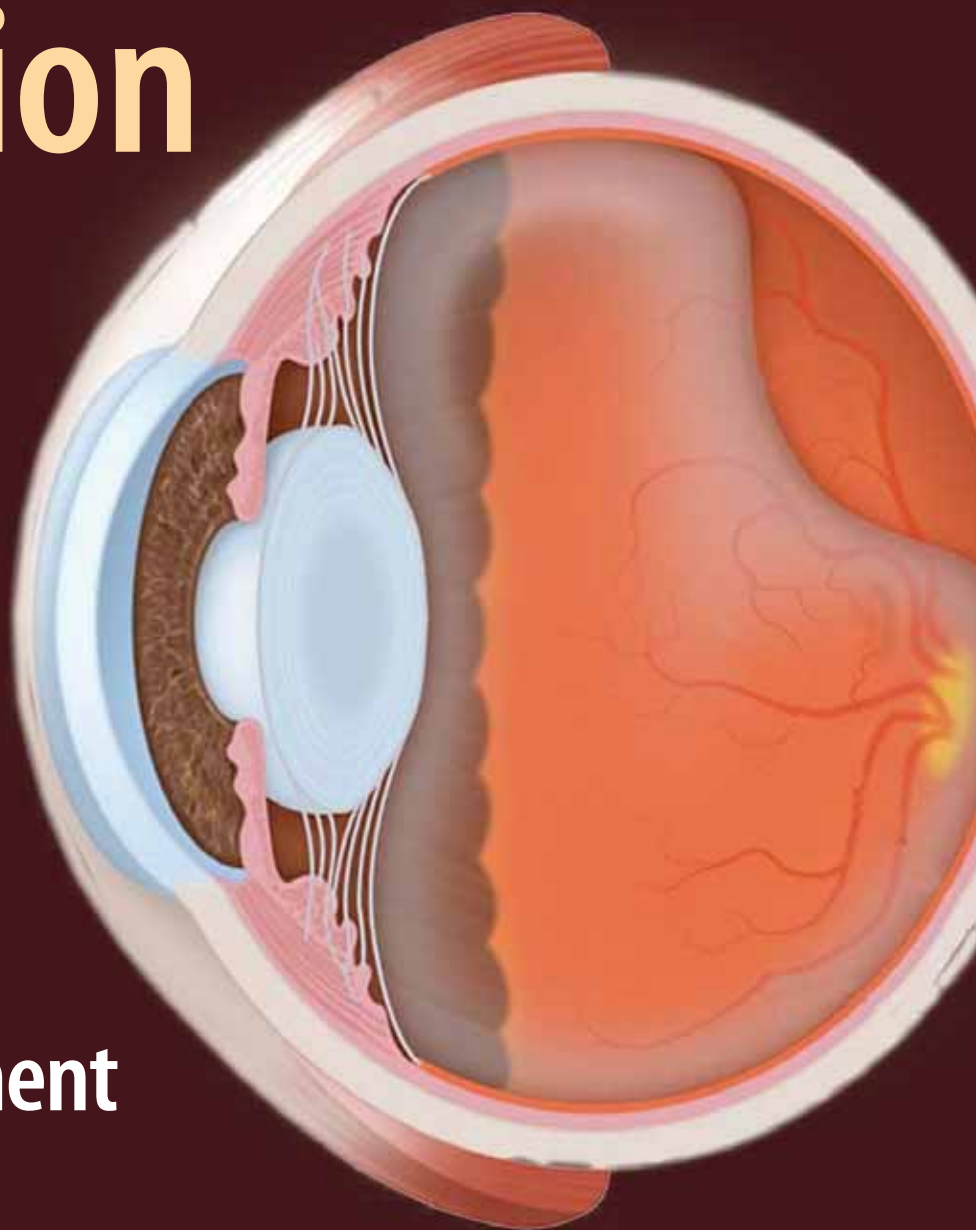


RETINA TODAY

Symptomatic Vitreomacular Adhesion

Diagnosis,
Pathologic
Implications,
and Management



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STATEMENT OF NEED

The goal of this continuing medical education (CME) supplement is to improve patient care by retina specialists and other ophthalmologists when they are managing symptomatic vitreomacular adhesion and traction.

Symptomatic vitreomacular adhesion is a condition when the vitreous gel adheres in an abnormally strong manner to the retina. VMA can lead to vitreomacular traction (VMT) and subsequent loss or distortion of visual acuity. Anomalous posterior vitreous detachment PVD is linked to several retinal disorders including macular pucker, macular hole, age-related macular generation (AMD), macular edema, and retinal tears and detachment.

The incidence of VMA has been reported to be as high as 84% in cases of macular hole; 74% in vitreomacular traction syndrome; and 56% in idiopathic epimacular membrane.¹ The incidence of VMA in macular edema appears to depend on the severity of the underlying condition.^{2,3} In AMD, the rates vary³⁻¹² but have been reported to be as high as 59% in exudative AMD.¹²

Currently, pars plana vitrectomy (PPV) is used to surgically induce PVD and release the traction on the retina for selected cases. A vitrectomy procedure, however, is not without risk. Complications with standard PPV¹²⁻¹⁵ and more recently with small-gauge PPV¹⁶⁻²⁰ have been reported and include retinal detachment, retinal tears, endophthalmitis, and postoperative cataract formation. Additionally, PPV may result in incomplete separation and it may potentially leave a nidus for vasoactive and vasoproliferative substances or it may induce development of fibrovascular membranes. Further, as is with any invasive surgical procedure, PPV introduces more trauma to the vitreous and surrounding tissues.^{21,22}

There are data showing that pharmacological induction of PVD using ocriplasmin (formerly known as microplasmin), a proteolytic human enzyme with activity against the protein matrix that comprises the vitreoretinal interface, has the following advantages over PPV: It induces complete separation, creates a more physiologic state of the vitreomacular interface, prevents the development of fibrovascular membranes, is less traumatic to the vitreous, and is potentially prophylactic.^{21,22} Additionally, vitreolysis obviates the costs associated with surgery and allows for earlier intervention, whereas surgery is reserved for more advanced cases. In two phase 3 studies, a single injection of ocriplasmin was shown to be safe and effective for PVD induction,^{23,24} providing further evidence that pharmacologic vitreolysis with ocriplasmin may provide an safe and effective alternative to PPV for inducing PVD.

To address these gaps, retina specialists and other ophthalmologists must master insights on the pathogenesis of VMA, the role that VMA plays in various retinal pathologies, and the benefits of induced PVD vs anomalous PVD. Mastery includes knowledge of the clinical implications of VMA and the results of recent clinical trials on both surgical and pharmacologic PVD induction, an understanding of vit-

reolysis agents and their differences, and the ability to identify patients who may benefit from PVD induction.

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TARGET AUDIENCE

This certified CME activity is designed for retina specialists and general ophthalmologists involved in the management of patients with retinal disease.

LEARNING OBJECTIVES

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

- Explain the process by which VMA occurs
- Identify the disease states with which VMA is associated
- Identify the clinical implications of anomalous PVD

- Identify the risks of performing vitrectomy to induce PVD
- Explain the mechanism of action of pharmacologic vitreolysis
 - Differentiate between the various agents that can be used for pharmacologic vitreolysis in terms of their composition, advantages, and disadvantages
 - Discuss the available data on the safety and efficacy of vitreolysis agents for PVD induction

METHOD OF INSTRUCTION

Participants should read the CME activity in its entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit <http://www.dulaneyfoundation.org> and click "Online Courses." Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 AMA PRA Category 1 Credit.[™] The estimated time to complete this activity is 1 hour.

ACCREDITATION AND DESIGNATION

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 Dulaney Foundation and *Retina Today*. The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this enduring material for a maximum of 1 AMA PRA Category 1 Credit.[™] Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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In accordance with the disclosure policies of the Dulaney Foundation and to conform with ACCME and US Food and Drug Administration guidelines, anyone in a position to affect the content of a CME activity is required to disclose to the activity participants (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices or providers of commercial services and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY CREDENTIALS



David M. Brown, MD, is the director of the Greater Houston Retina Research Center and practices at Retina Consultants of Houston and the Methodist Hospital in Houston, TX. He is a member of the *Retina Today* Editorial Board.



Pravin U. Dugel, MD, is Managing Partner of Retinal Consultants of Arizona in Phoenix; Clinical Associate Professor of Ophthalmology, Doheny Eye Institute, Keck School of Medicine at the University of Southern California, Los Angeles; and

Founding Member of the Spectra Eye Institute in Sun City, AZ. He is a member of the *Retina Today* Editorial Board.



Mark S. Humayun, MD, PhD, is Professor of Ophthalmology, Biomedical Engineering, Cell and Neurobiology, Keck School of Medicine of the University of Southern California and is Associate Director of Research at the Doheny Retina Institute in Los Angeles.



Peter K. Kaiser, MD is Professor of Ophthalmology at the Cleveland Clinic Lerner College of Medicine and a staff surgeon in the Vitreoretinal Department at the Cole Eye Institute, Cleveland Clinic. He is the Founding Director of the Digital Optical Coherence Tomography Reading Center (DOCTR) at the Cole Eye Institute. He is a member of the *Retina Today* Editorial Board.



Michael T. Trese, MD, is Clinical Professor of Biomedical Sciences at The Eye Research Institute of Oakland University, Clinical Associate Professor at Wayne State University School of Medicine, and Chief of Pediatric and Adult Vitreoretinal Surgery at William Beaumont Hospital.

FACULTY/STAFF DISCLOSURE DECLARATIONS

David M. Brown, MD, reports that he receives financial support from Alcon, Alimera, Allergan, Eli Lilly, Genentech, Molecular Partners, Ophthotech, Paloma, Regeneron, Steba Biotech, and Thrombogenics; honoraria and/or travel reimbursement from Allergan, Genentech, and Regeneron; and is a consultant to Alcon, Alimera, Allergan, Genentech, Molecular Partners, Paloma, Regeneron, Steba Biotech, and Thrombogenics.

Pravin U. Dugel, MD, reports that he is a consultant to Abbott Medical Optics, Alcon, Allergan, Arctic Dx, Bausch + Lomb, Genentech, Macusight, Neovista, ORA, QLT, Regeneron, and Santen.

Mark S. Humayun, MD, PhD, reports that he is a consultant to, shareholder of, receives honoraria and/or travel reimbursement from, and holds patents with Second Sight Medical Products.

Peter K. Kaiser, MD, reports that he is a consultant to Alcon, Arctic Dx, Bausch + Lomb, Bayer, Genentech, Kang Hong Biotech, Novartis, Ophthotech, Oraya, and Regeneron; and is a shareholder in SKS Ocular.

Michael T. Trese, MD, reports that he is an investor/shareholder with Nu-Vue Technologies; holds patents with Nu-Vue Technologies, and Thrombogenics; and is a consultant to Synergetics.

All of those involved in the planning, editing, and peer review of this educational activity report no financial relationships.

Symptomatic Vitreomacular Adhesion (VMA): Diagnosis, Pathologic Implications, and Management

Michael Trese, MD: Vitreomacular adhesion (VMA) is a condition when the vitreous gel adheres in an abnormally strong manner to the retina. VMA can lead to vitreomacular traction (VMT) and subsequent loss or distortion (metamorphopsia) of visual acuity, a condition known as symptomatic VMA. VMA occurs in the context of an incomplete or anomalous posterior vitreous detachment (PVD) and is linked to several retinal disorders including macular hole, epiretinal membrane (ERM), neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), retina vein occlusion (RVO), and retinal tears and detachment.¹

SYMPTOMATIC VMA AND ANOMALOUS PVD

Dr. Trese: Dr. Brown, can you explain the process by which VMA and anomalous posterior vitreous detachment (PVD) occurs?

David M. Brown, MD: The simplest way to explain the process of VMA and anomalous PVD is how I explain it to my patients. I tell them that there is a gel inside the eye and that as a person gets older, the gel degenerates and clumps up creating floaters. Eventually the gel structure cannot keep its shape as a Jello ball, and it collapses in on itself. The vitreous gel is connected to the retina similar to Velcro and the adhesion is usually strongest at the optic nerve and at the fovea. When it pulls on the optic disc, it does not create much of a problem, but when it pulls on the fovea, the most delicate part of the photoreceptors and the thinnest part of the retina, it can create a macular hole, which requires surgical intervention.

Peter K. Kaiser, MD: Most of us will eventually develop a posterior vitreous separation as a result of age, which involves both liquefaction of the vitreous as well as release of the vitreous from the retina. If the vitreous



“Vitreomacular adhesion occurs in the context of an incomplete or anomalous posterior vitreous

detachment and is linked to several retinal disorders.”

— *Michael T. Trese, MD*

liquefies and releases uniformly and in a synchronized manner, the result is a successful PVD; however, if VMA develops in the foveal region, the result can include macular hole, macular traction, vitreomacular traction syndrome (VMT), and in patients with diabetes, posterior hyaloid traction.

Pravin U. Dugel, MD: We are beginning to understand that a PVD is not as simple as we once thought it was. It is important to note, as Dr. Kaiser stated, that there are two distinct steps that occur: liquefaction, or synesis, and separation of the interface, or syneresis, and if that two-step process does not occur in proper synchrony and completion, anomalous PVD can result, leading to VMA.

Years ago, Jerry Sebag, MD, talked about a unifying concept in anomalous PVD.¹ A VMA resulting from anomalous PVD can go one of two ways. The vitreous can actually split to form a schisis and a partial thickness PVD, resulting in traction. If the traction goes outward, a macular hole may result. If the traction goes inward, an epiretinal membrane (ERM) or macular pucker may form. A full thickness separation of the vitreous may occur, but it may be caught up somewhere. If it is caught in the posterior pole, and posterior trac-

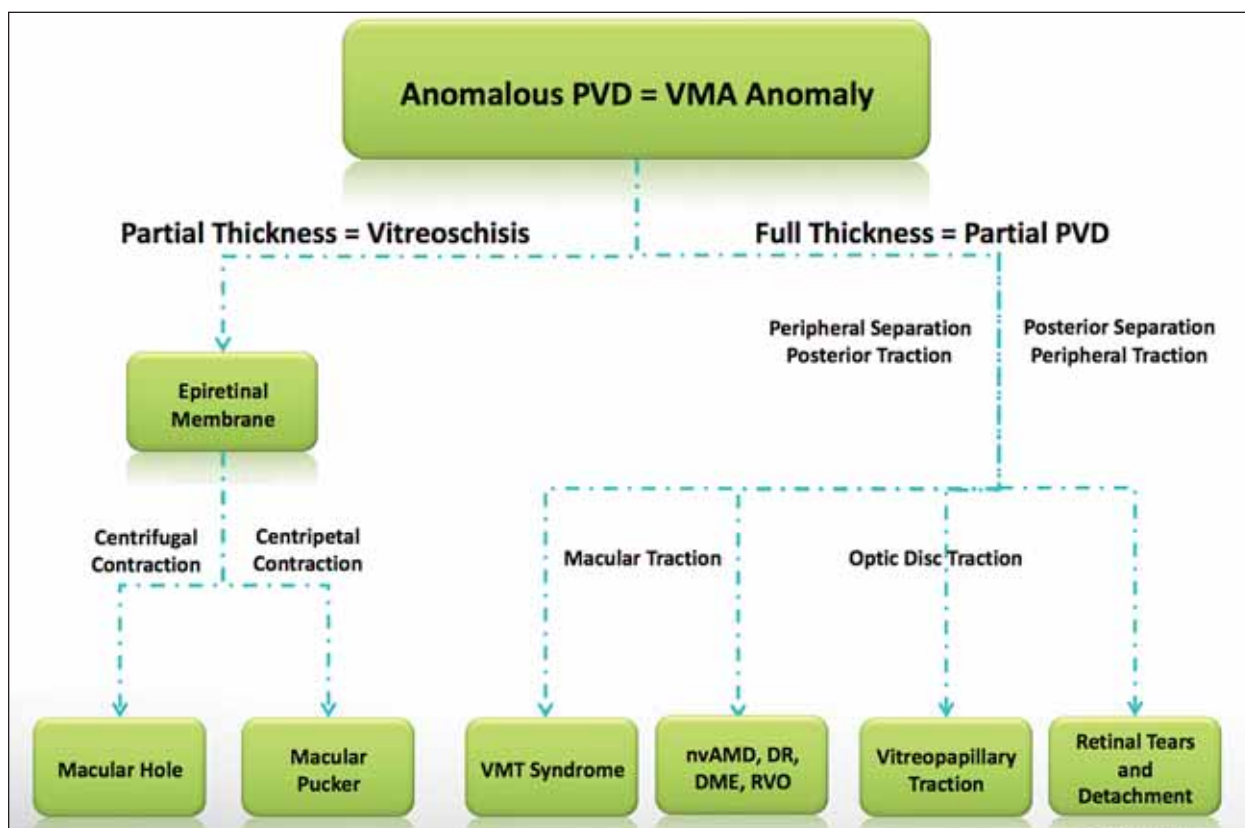


Figure 1. The implications of anomalous PVD.

(Information courtesy of Jerry Sebag, MD)

tion occurs with peripheral separation, macular traction may result. Macular traction can cause vitreomacular traction syndrome, but it is also linked to many other conditions such as neovascular AMD, diabetic retinopathy, DME, and RVO. If traction occurs at the optic disc, vitreopapillary syndrome, and ensuing disc edema, can occur, and if there is posterior separation but peripheral traction, retinal tears and retinal detachment can occur (Figure 1).

It is interesting to see how VMA resulting from anomalous PVD is involved in so many diseases—I think that we are gaining more understanding because our imaging techniques are now married with what we know about the pathophysiology of this process.

Mark Humayun, MD: In the era of optical coherence tomography (OCT), which allows for easier detection of macular adhesions, what is the definition of symptomatic VMA? Perhaps we can see distortion of the retina on our OCT scans, but the patient may or may not attribute their symptoms to this condition. It is interesting, particularly in an age where we are able to see these adhesion areas much better.

Dr. Trese: The diagnosis of PVD, which we all have on our diagnostic sheets, is really an exclusion of a retinal tear. How many times have each of us seen a patient who presents with flashes and floaters and diagnosed PVD, only to have the patient come back 2 years later with flashes and floaters, leading to the realization that the rest their vitreous has probably separated? As previously stated, there are two separate concepts that are involved in the change in the vitreous—liquefaction and separation. Liquefaction is a core change and separation is a vitreoretinal juncture change. If the core change occurs without the juncture change, or the two do not take place relatively close in time to one another, anomalous PVD and subsequent VMA leading to traction and associated symptoms can occur.

Dr Kaiser: Anomalous PVD is really any time liquefaction and separation do not occur at the same time. If the liquefaction develops without the release, symptomatic VMA or a tear in the periphery can result.

Dr. Trese: If you look at the dispace study, which evaluated this agent that liquifies the vitreous without

Chemical Vitreous Manipulation May Represent New Frontier in the Treatment of Retinal Disease of Wet AMD

Ocriplasmin, a bioengineered truncated form of the human plasmin molecule, has proved effective in providing resolution of vitreomacular adhesion (VMA) and improving visual acuity and function when compared to placebo injection in two large phase 3 studies.

Pravin U. Dugel, MD, presented the pooled data from MIVI-6 and MIVI-7 during the Institut de Microcirurgia Ocular Trends in Surgical and Medical Retina Meeting in Barcelona.¹ Dr. Dugel said that 26.5% of patients achieved the primary endpoint of pharmacologic VMA resolution at day 28 after one injection of ocriplasmin, with approximately 75% of these patients experiencing resolution within 1 week of injection. Enrollment criteria for the trials did not exclude patients with epiretinal membrane (ERM). "If you look at patients who did not have an ERM with one injection alone, 37.4% achieved this end goal of resolution of VMA. If you look at patients with an ERM, 8.7% had resolution of VMA, which is also statistically significant."

Toward the secondary endpoints, 13.4% of patients achieved complete posterior vitreous detachment (PVD) and 23.7% and almost 10% gained two or three lines of vision or more, respectively. Over 40% of patients with full-thickness macular hole had closure after a single injection. For macular holes smaller than 250 μ m, however, this increased to almost 60%, said Dr. Dugel. Visual function and quality of life parameters were also favorable in the

groups that received ocriplasmin injection. The safety profile of ocriplasmin was favorable in both phase 3 studies, according to Dr. Dugel.

Although the mechanisms of PVD appear simple, the process is complicated, requiring the steps of liquefaction and separation of the vitreous from the retina to be synchronized, said Dr. Dugel. Abnormal VMA and subsequent partial PVD can lead to vitreomacular traction (VMT) syndrome, resulting in metamorphopsia and decreased vision. Many patients with VMA, however, present with relatively good visual acuity. "For these patients, we just watch and wait, because the risk/benefit ratio of vitrectomy, currently the only treatment available, will be too large," said Dr. Dugel. "However, these patients come to our office unhappy and leave our office unhappy."

VMA is implicated in a variety of retinal diseases, including macular hole, neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), retinal vein occlusions (RVO), and vitreopapillary syndrome, said Dr. Dugel, and improved imaging may allow for earlier detection of VMA. "Chemical vitreous manipulation has the potential to have a major effect on clinical practice," he concluded.

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causing vitreous-retina interface separation, the retinal detachment rate was approximately 5%, which highlights the danger of inducing liquefaction without manipulation of the vitreoretinal juncture.²

Dr. Brown: Both liquefaction and syneresis occur naturally as the eye ages. Disease processes, however, such as diabetes and AMD, cause exudation and make the retinal interfaces thicker and harder to break. Thus, there may be a higher incidence of anomalous PVDs as the gel needs to pull away in these eyes, resulting in more pathology.

Dr. Trese: In the case of diabetes, hyperglycemia alone increases laminin and fibronectin, two of the three components in the vitreoretinal juncture as well as the

glomerular extracellular matrix, tightening the vitreoretinal juncture and reducing the filtration rate from the kidneys.

Dr. Humayun: There are many different ways to think about VMA. Most of us know that the macula is the area we are trying to protect from developing neovascularization, hemorrhage, or macular edema. We also know that vitreous is adherently attached to the optic nerve and along the vessels and can create VMT. This interface is complex—it can have both fibrous and cellular components. As we better understand the retinal interface, it is becoming clear that it plays a role in many retina diseases, particularly when there is traction on the retina.

It would be advantageous to use the tools we currently have to perform an optical-imaging biopsy with OCT

under dynamic conditions to better understand the mechanical functions.

PHARMACOLOGIC VITREOLYSIS

Dr. Trese: How would you define pharmacologic vitreolysis?

Dr. Brown: Pharmacologic vitreolysis or pharmacologic vitreodynamics is the process by which an enzyme is used to mechanically change the vitreous. This involves two distinct mechanisms. One mechanism is liquefaction of the core vitreous and the other is degradation of the vitreoretinal interface. By doing this we change not only the physical traction where the “Velcro” is trying to separate from the retina, but also changes in the milieu with the oxygenation and chemical balance that go along with this separation of the vitreous from the retina.

Dr. Trese: What is the role of the vitreous in disease states such as AMD, DME, and RVO?

Dr. Dugel: It may be too early to tell, but there are some articles that are coming out that are compelling. A study from Susan Binder, MD’s, group showed that PVD may be protective against AMD, whereas VMA may promote exudative AMD.³ Another earlier paper from Dr. Binder’s group demonstrated that persistent PVD may be a risk factor for exudative AMD from inflammation-induced vitreoretinal traction.⁴

The role of the vitreous in disease states like AMD is interesting. Obviously, we have an unsustainable model in our current monotherapy treatment of AMD with injections of anti-VEGF, and I think that we can all agree that combination therapy is an improvement on monotherapy. However, we have just recently started talking about manipulation of the vitreous and how this may play an important role in disease management.

Your group published an animal study regarding the effect of bevacizumab on vitreous detachment.⁵ A study such as this, which evaluates the effects of pharmacologic agents on vitreous manipulation, may have important implications.

Dr. Kaiser: It is difficult to grasp the extent of the vitreous’ role once a patient has developed choroidal neovascularization (CNV) and AMD. There is clearly a strong association, as evidenced in the literature.^{3,4,6,7} The question that remains, however, is if CNV is already present, would inducing vitreous separation alleviate symptoms or enhance the effect of an anti-VEGF agent to decrease the number of injections needed?



“We have just recently started talking about manipulation of the vitreous and how this may play an important role in disease management.”

— Pravin U. Dugel, MD

Dr. Trese: Dr. Dugel, can you describe the enzymatic agent, ocriplasmin (ThromboGenics), formerly known as microplasmin that has been under study for pharmacologic vitreolysis for symptomatic VMA?

Dr. Dugel: Ocriplasmin is a truncated form of human plasmin. Ocriplasmin is not a new drug—it has been in development for many years and there are excellent phase 1 and phase 2 studies that were previously encouraging. The phase 3 studies, which were two large multicenter, prospective, randomized trials, were remarkably consistent in regard to the safety and efficacy outcomes.^{8,9} As far as clinical use is concerned, this drug was tested in a diverse population of patients with diseases such as VMT, macular hole, and ERM (See “Key Published Literature”). The applicability, however, will extend far beyond these diseases. It will go to other diseases where VMT may be involved such as DME and neovascular AMD. It will also extend to the combination of ocriplasmin with other drugs such as anti-VEGF agents; there is now evidence that this drug may make anti-VEGF treatments more effective when used in combination.⁵ Finally, I think this drug will also be used as an adjunct to surgery. The potential of injecting this drug the day before surgery and making a very complicated case much easier is intriguing. In general, I think that we have a great deal of evidence regarding this drug but the potential clinical applications of pharmacologic vitreolysis may be enormous.

POTENTIAL APPLICATIONS FOR VITREOLYSIS

Dr. Brown: One of the unmet medical needs in terms of classic VMT is for patients with impending macular hole but relatively good visual acuity, placing the surgeon on the fence as to whether to operate sooner or later. To have an agent for vitreolysis would help a fair number of our patients avoid surgery completely.

Dr. Kaiser: You could take it even one step further. Patients with so-called stage zero macular holes where the fellow eye has a gull-wing shaped vitreous coming

Pharmacologic Vitreolysis: Key Published Literature

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down to the fovea but no hole and no true traction may be a higher risk for developing a bilateral hole some time in the future.¹⁰ Should we treat these patients with a vitreolysis agent as prophylaxis for a potential future problem?

Dr. Trese: Gull-shaped retinal detachments create a large amount of traction. Lois Smith, MD, PhD, told me about an individual in the lab at Children's Hospital Boston who has demonstrated that isolated traction on Muller cells can generate VEGF. I am not sure what role vitreoretinal adhesion plays in AMD, but I agree that it is most likely early in the process. Once CNV is present, we need to study if cleaving the adhesion will help.

Dr. Dugel: I also see potential for vitreolysis agents as adjuncts to surgery. Some of the hardest cases we see are complicated tractional retinal detachments in diabetics and retinal detachments in pediatric patients. If we can inject a vitreolysis agent a day prior to surgery, it might make the surgery easier and more successful.

Dr. Brown: There is postulation that schisis pockets can act as a sink for VEGF. We know that after a PVD there is more oxygenation, so a PVD would be ideal for every patient with diabetes. Even when the glycosylated hemoglobin is causing vascular damage, you want more oxygen for the retina and a better escape for any ischemic factors. I do not see any reason not to induce a PVD as long as I have an agent that is effective and safe.

Dr. Kaiser: Assuming we had a drug that is effective and safe, it would be best to induce PVD prior to the development of exudation and protein release that increases adherence, because after these occur, it will become more difficult to release the junction. So I think you can argue that it is reasonable to inject with ocriplasmin when mild changes become apparent to prevent future complications.

Dr. Dugel: Because we know a lot more about the role of the vitreous in diabetes than we do in AMD, we are more apt to argue for early injection. The safety profile of ocriplasmin was shown to be excellent in the phase 3 trials.^{8,9} In fact, there were more cases of retinal tears and detachments in the placebo group than in the drug group, so these were most likely complications of vitrectomy.

Dr. Trese: Let's say that sometime in the future you have a patient with a 9-year history of diabetes who has a couple of dot and blot hemorrhages and no PVD on



"I do not see any reason not to induce a PVD as long as I have an agent that is effective and safe."

— David M. Brown, MD

OCT or ultrasound. What do you do if, after injecting ocriplasmin, a PVD does not result? Peter Stalmans, MD, presented data from the phase 2 ocriplasmin study on a group of patients with diabetes. He injected the enzyme in these patients, many of whom had proliferation and had undergone laser and approximately 11% to 14% cleaved. In my opinion, this is a miracle because there was no case selection.¹²

If you did not have a PVD in such a patient, would you reinject?

Dr. Dugel: I would reinject. Regarding the data to which you refer from the phase 2 trials, there was one cohort of nine patients for whom reinjection was allowed. Although the group was small, the rate of PVD after reinjection was almost 60%.¹² Given the very strong safety profile of ocriplasmin in over 800 eyes, I would not hesitate to inject two or three times.

Dr. Kaiser: The phase 3 study did not look at reinjection, but I think that it is important to consider that maybe the first injection is just not getting the drug to the right location. With a second or third injection, you will certainly increase the likelihood of getting it to the right place and being able to cleave the junction. If and when ocriplasmin is approved by the US Food and Drug Administration, a good investigator-sponsored trial might include an analysis of reinjection data.

Dr. Trese: Another scenario where vitreous manipulation may be justified is in cases of capillary dropout in retinal vein occlusion. Injecting ocriplasmin could help to re-establish circulation in some of these cases.

Dr. Dugel: Our whole way of thinking of neovascularization might change if we could use vitreous manipulation to affect circulation. Currently, in patients with ischemia from any cause, we have no effective treatment. It would be very valuable to have a drug that could increase circulation by chemical vitreous manipulation. This is plausible: there is good evidence, originally from

Stefansson, that mechanical vitreous removal increases oxygenation.¹³

Dr. Trese: Imagine that you are examining a patient who has VMT due to VMA without a membrane, a macular hole with less than a 1,500- μ m attachment, and lattice degeneration in the periphery. How do you handle this case?



“Vitrectomy is certainly an excellent way to fix symptomatic VMAs, but if a safer, quicker way exists to do it, it is better for the patient.”

— Peter K. Kaiser, MD

Dr. Brown: Because the induction of a PVD might very well increase the risk of a peripheral tear in this patient with peripheral lattice, I would probably demarcate the peripheral lattice degeneration lesions with thermal laser at least 3 or 4 days prior to injecting an agent to induce pharmacologic vitreolysis. In the ocriplasmin clinical trials at our site, I did not have any cases of retinal tearing, but we did not have many patients with peripheral pathology.

Dr. Trese: One of the first patients treated in the clinical trials in Europe did have a retinal tear. The clinician who was treating the patient did not see any sign of lattice degeneration in the periphery. However, after being treated with laser, they did well. Although the tear rate was not high in the clinical trials, it is something that we need to think about.

Dr. Kaiser: Although I do not consider lattice degeneration a contraindication for ocriplasmin injection, it is important to discuss the risks of retinal tears with your patients. It is important to conduct a thorough exam prior to considering this type of injection, and if lattice degeneration is detected, the option of treating with laser prior to injection vs just injection should be discussed. Additionally, patients should be counseled on symptoms of retinal tear, should it occur.

MAXIMIZING THE MECHANICAL AND BIOCHEMICAL ACTIVITY OF OCRIPLASMIN

Dr. Dugel: The size of the VMA is directly related to how well ocriplasmin works. Additionally, the location of the injection is important. If it is injected away from

the pathology, it will be hard for the drug to reach the location of the adhesion.

Dr. Trese: If you look at the 250- μ m adhesions from the MIVI-TRUST phase 3 clinical trials for ocriplasmin, there were approximately 60% of these adhesions that cleaved.^{8,9} For those that were 1,500 μ m or larger, the numbers that cleaved were small. How do you assess this clinically? First, as Dr. Dugel said, delivery of the enzyme is critical to get the ocriplasmin to where it can work.

We presented a poster at the Association for Research in Vision and Ophthalmology 2011 meeting that shows a technique that attempts to achieve a larger area of drug from the same bolus. We found that when injecting India ink with a 30-gauge quadraport needle, as compared to a standard 30-gauge needle to inject India ink, the ink spread more quickly and to a wider area, whereas the ink accumulated around the tip of the standard 30-gauge needle.¹¹

In another group of animals injected with ocriplasmin and plasmin using a standard 30-gauge needle vs the quadraport 30-gauge needle, scanning electron microscopy at 1 week showed that there was no residual enzyme on the internal limiting membrane with the quadraport needle.¹¹

Dr. Dugel: Achieving needle delivery that will allow for selective infusion of the drug to the site where it is needed is a challenging task. Approximately 14% of patients and 20% of patients without an ERM treated with ocriplasmin in the pivotal phase 3 trials achieved the secondary endpoint of total PVD induction.^{8,9}

Dr. Humayun: Mechanically speaking, the idea of injecting in different places, lifting the attachment, and eventually making the entire sheet come off seems to make sense.

Dr. Brown: So you are saying is that after injecting ocriplasmin in several locations, if you lift up one edge and you move it back and forth, this may be of benefit and a more gentle vitreolysis?

Dr. Dugel: Actually, sequential injections may be easier. We have some data on this from the phase 2 trials regarding these from one cohort in which this was allowed, and it was shown that sequential injections may increase the rate of total PVD without having to move the patient's eye.

Dr. Trese: When discussing how to maximize mechani-

cal and biochemical activity, reliable imaging may enhance the ability to target exactly where you want to inject the enzyme. The dynamic SD-OCT imaging that we have with the Spectralis (Heidelberg Engineering, Carlsbad, CA) offers a better image of the vitreous so that we can better understand its relationship to retinal disease.

We have put together a procedure room to perform the injections of ocriplasmin that allows us to do the injection through an operating microscope. It would be ideal to be able to do these injections in an OCT-guided manner.

Dr. Kaiser: You already have half of the system in place. In the future, microscopes with built-in OCT systems will be available. Currently, the Bioptigen Spectral Domain Ophthalmic Imaging System (SDOIS; Research Triangle Park, NC) has a mount for most microscopes, and Carl Zeiss Meditec (Dublin, CA) is working on a version of microscope with OCT that is built in. The ability to see underneath the vitreous during injection is imminent.

Dr. Brown: What do we know of the diffusion of ocriplasmin?

Dr. Trese: The way that ocriplasmin works is that it takes one bite and then it either binds to substrate or consumes itself. So if you inject it in a large bolus through a standard needle it consumes substrate and then itself. If you use a multiport needle, however, such as the quadraport needle that was used in our study, the chances of getting more substrate are higher.

CHANGING TREATMENT PARADIGMS

Dr. Trese: This has been an interesting year in retina. We learned the results of the Comparison of AMD Treatments Trial, which showed that an inexpensive anti-VEGF agent, bevacizumab (Avastin, Genentech) is noninferior to a very expensive anti-VEGF agent, ranibizumab (Lucentis, Genentech). We also have results from the two large clinical trials showing the safety and efficacy of VEGF trap (Eylea, Regeneron), although we do not know how this drug will be priced when and if it is approved.

How do you think that physicians feel about something that takes away few of the surgical procedures that they enjoy performing and that may represent another expensive drug to handle in the office?

Dr. Kaiser: As physicians, we all have the same goal: to treat patients in the best and safest way we can.



“In ophthalmology, when a noninvasive option becomes available we typically intervene earlier.”

— Mark S. Humayun, MD, PhD

Vitrectomy is certainly an excellent way to fix symptomatic VMAs, but if a safer, quicker way exists to do it, it is better for the patient.

Dr. Dugel: I agree. However, there are many instances where surgery is still indicated. In the clinical trials for ocriplasmin, there was almost a 60% closure rate of macular hole with a single injection if the hole was 250 μm or smaller.^{9,10} But if in the case of a large macular hole with no VMA, there is no reason to inject ocriplasmin; we still need to perform surgery.

Another consideration is that this drug may actually enhance our surgery. I can picture using this drug for complicated traction detachment or for a young patient who requires a PVD, so I do not think that pharmacologic vitreolysis is going to take away from our surgery. Also, in patients with ERM, ocriplasmin will help to resolve part of the problem; symptoms associated with VMA leading to anteroposterior traction. We will still have to perform surgeries to relieve the tangential forces exerted by an ERM. In fact, I think ocriplasmin will be a safe and effective alternative for patients who currently have no treatment options, patients with VMA and early symptoms, and will be an effective adjuvant for difficult surgical cases, making us better surgeons. I do not see push back of this drug from surgeons. On the contrary, I predict surgeons will see the potential beneficial effect of this drug for our patients in the office and in surgery and will welcome access to it.

Dr. Humayun: In ophthalmology, when a noninvasive option becomes available we typically intervene earlier. Ocriplasmin will allow us to treat patients in whom there clearly is pathology and who are symptomatic but for whom surgery is not indicated because of the poor risk/benefit ratio. I do not think that there is much overlap with surgery, particularly when you are talking about earlier disease.

Dr. Trese: I think that eventually, criteria for early intervention for symptomatic VMA with ocriplasmin will be developed. I imagine that the American Academy of

Ophthalmology will produce guidelines based on high-resolution OCT imaging to help physicians in using this drug effectively.

SUMMARY

Dr. Kaiser: The ability to treat symptomatic VMA, particularly early macular holes, with pharmacologic vitreolysis offers an efficient and safe way to improve our patients symptoms without requiring surgery or face-down positioning. Moreover, the therapy may help us if surgery is required in the future, as the vitreous is more liquefied and easier to peel.

Dr. Brown: The addition of ocriplasmin will be a welcome addition to the armamentarium of vitreoretinal surgeons. The agent will be first used in patients with impending macular holes and small holes with persistent VMT at the edges. If multiple injections (or novel injection techniques) can result in reliable pharmacologic vitreolysis, I can easily see the agent being used routinely before vitreoretinal surgery and possibly as a prophylactic agent in diabetic patients prior to the development of proliferative disease.

Dr. Humayun: As the field of enzymatic vitreolysis continues to advance and FDA-approved methodologies become available, there is no doubt that such an approach will be used to treat symptomatic VMA.

Dr. Dugel: There are three forces that I believe will come together to make ocriplasmin a very valuable drug for the retina specialist. The first force is the

advent of technological advances with OCT that allow us to easily visualize VMA. The second force is that all retina specialists are adept at performing an intravitreal injection. The third force is that we currently employ a watch-and-wait strategy for many of our patients due to the lack of options for a safe, noninvasive procedure. If ocriplasmin becomes available, I believe that retina practices are prime to adopt this agent for pharmacologic vitreolysis. ■

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Symptomatic VMA: Diagnosis, Pathologic Implications, and Management

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CME QUESTIONS

1. Effective posterior vitreous detachment (PVD) requires that vitreous liquefaction and separation from the retina occur _____.

- a. simultaneously
- b. in a synchronized manner
- c. quickly
- d. none of the above

2. Symptomatic vitreomacular adhesion (VMA) can cause:

- a. distorted vision
- b. retinal tear
- c. macular hole
- d. all of the above

3. A total of ____% of patients in the MIVI-6 and MIVI-7 studies achieved the primary endpoint of pharmacologic resolution of VMA.

- a. 51.1
- b. 26.5
- c. 49.9
- d. 15.5
- e. none of the above

4. Anomalous PVD may have a role in the following diseases:

- a. macular pucker
- b. macular hole
- c. AMD
- d. DME
- e. RVO
- f. all of the above

5. In the phase 3 trials, almost 60% of patients with macular holes of what size had closure after a single injection of ocriplasmin?

- a. 450 μ m or smaller
- b. 150 μ m or smaller
- c. 200 μ m or smaller
- d. 250 μ m or smaller
- e. none of the above

6. The phase 3 clinical trials evaluated ocriplasmin in connection with the following disease states:

- a. AMD
- b. DME
- c. macular hole
- d. RVO
- e. all of the above

Symptomatic VMA: Diagnosis, Pathologic Implications, and Management

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