Symptomatic Vitreomacular Adhesion

Statement of need

Symptomatic vitreomacular adhesion is a condition in which 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; 100% 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 vary4-11 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 with any invasive surgical procedure, PPV introduces trauma to the vitreous and surrounding tissues.21,22

There are data showing that nonsurgical induction of PVD using ociprilasmin, a vitreolysis agent, can offer the benefits of successful PVD while eliminating the risks associated with a surgical procedure. Pharmacologic vitreolysis 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 earlier intervention, whereas surgery is reserved for more advanced cases. In 2 phase 3 studies, a single injection of ociprilasmin was shown to be safe and effective for PVD induction,23,24 providing further evidence that pharmacologic vitreolysis with ociprilasmin may provide a safe and effective alternative to PPV for inducing PVD. Retina specialists and other ophthalmologists must be educated on this new treatment for symptomatic vitreomacular adhesion.

To address these educational 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 vitreolysis agents and their differences, and the ability to identify patients who may benefit from PVD induction.

*Ociprilasmin has been granted priority review by the US Food and Drug Administration, but is not yet available in the United States.

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:
1. explain the process by which VMA occurs;
2. identify the disease states with which VMA is associated;
3. identify the clinical implications of anomalous PVD;
4. identify the pros and cons of a surgical vitrectomy vs. pharmacologic vitreolysis to induce PVD;
5. explain the mechanism of action of pharmacologic vitreolysis;
6. differentiate between the various agents that can be used for pharmacologic vitreolysis in terms of their composition, advantages, and disadvantages; and
7. 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.

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FACULTY/STAFF DISCLOSURE DECLARATIONS
Dr. Dugel states that he is a consultant to Alcon, AMO, Macusight, Neovista, ArcticDx, Ora, Regeneron, and ThromboGenics; and is a minor shareholder in Macusight and Neovista.

Dr. Williams states that he is a consultant to Genentech.

Dr. Murray states that he is a consultant to Alcon Laboratories Inc. and ThromboGenics.

Dr. Regillo states he receives research grant support from Alimera, Allergan, Genentech, GlaxoSmithKline, Regeneron, ThromboGenics, ACT, Johnson & Johnson, and QLT, and that he is a consultant to Alimera, Genentech, Regeneron, GlaxoSmithKline, and Alcon Laboratories Inc.

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

Advanced imaging and a new pharmacologic solution have changed the way we think about this condition.

BY PRAVIN U. DUGEL, MD

Posterior vitreous detachment (PVD) is largely viewed as a fairly simplistic event; however, this is not necessarily the case. PVD is composed of 2 biologic phases that must work in synchrony—liquefaction of the vitreous and separation of the vitreous from the retina. If these 2 phases do not work in synchrony, a normal vitreous detachment will not occur. Instead, what results is known as an anomalous, or pathologic, vitreous detachment and vitreomacular adhesion (VMA), in which an area of attachment of the vitreous exists where it should not. VMA at the macula causes metamorphopsia, or visual distortion.

Historically, we have had agents that can induce 1 phase of the PVD, but again, liquefaction and separation must occur in synchrony. Hyaluronidase was first introduced in 1943 and was more recently reintroduced as Vitrase (Ista). This agent did not work well because it achieves only liquefaction, not separation. Another agent, dispase, which is a cleaving agent, also did not work well because, conversely, it causes interface separation without liquefaction. Ocriplasmin (ThromboGenics) is the only agent that induces both liquefaction and separation of the vitreous from the retinal interface.

Currently, for most patients with VMA who maintain good vision, the only reasonable available option is observation, due to the risks involved with a surgical intervention. This can be frustrating to patients because they come to our offices with true symptoms of poor vision and distortion and, because we can do nothing for them, they leave unhappy.

By choosing watchful waiting, we are hoping for spontaneous separation of the vitreous from the retina. As David Williams, MD, MBA, discusses in his article beginning on page 6, however, spontaneous separation is a relatively rare event. Rather, what seems to happen more frequently is vitreomacular traction (VMT), resulting in cystic and retinal pigment epithelium changes and subsequent visual acuity loss. Macular hole is another possible consequence of VMA that is left to observation.

ADVANCED IMAGING AND VMA

The condition in the top panel of Figure 1 can be described by a number of names: VMT, stage 1 macular hole, or macular cyst. Therefore, the lack of accuracy of our nomenclature betrays continued understanding of this condition.

Because we now have access to advanced imaging techniques, from time-domain optical coherence tomography (OCT) to spectral-domain (SD) OCT, we are further ahead in our understanding of VMA, VMT, and macular hole. Our
nomenclature, however, lags far behind, which can lead to confusion and misunderstanding. It is quite formidable to think of how far we have come with our imaging technology. When I performed my medical retina fellowship with J. Donald M. Gass, MD, he was using a Hruby lens, which no one else was using at the time, and was able to see pathology in an unprecedented fashion. Imagine what he could have done using our current imaging technologies.

Even with older time-domain OCT, it is apparent that VMA plays a larger role in retinal disease than was previously understood. The advances in OCT technology are related to an increased understanding as to the prevalence of VMA. SD-OCT has allowed improved visualization of the vitreoretinal interface and has revealed the larger role that VMA plays in retinal disorders such as age-related macular degeneration, diabetic retinopathy, epiretinal membrane, cystoid macular edema, and retinal vein occlusion (RVO).

Based on this new understanding, a new ICD-9 diagnostic code 379.27 was designated for VMA.

APPLYING PHARMACOLOGIC VITREOLYSIS

Figure 2 shows a patient with 20/30 vision and metamorphopsia. Although this patient might complain about poor vision, I would not consider surgery because the vision is too good and so the benefits of surgery do not outweigh the risks. This patient, in my opinion, would be a perfect candidate for ocriplasmin.

I would also use ocriplasmin in a patient with a full-thickness macular hole, or for a patient who has VMA causing a macular cyst or a stage I macular hole.

For patients with RVO and macular edema, I would consider using ocriplasmin to increase the sustainability of anti-VEGF injections.

Figure 2. VMT; visual acuity of 20/30.

Even with older time-domain OCT, it is apparent that VMA plays a larger role in retinal disease than was previously understood.

SUMMARY

Currently, we have a convergence of several forces, 2 of which I have discussed. The first is the increased understanding of the role that the vitreous plays in retinal disease, fueled by advances in ocular imaging. The second is the availability of an agent that can achieve what could only be achieved previously by a surgical procedure. More data on all the available approaches to symptomatic VMA, along with information that shows its role in other retinal disease states, will be discussed in the following pages.
When considering anomalous posterior vitreous detachment (PVD) and vitreomacular adhesion (VMA), it is useful to have some sort of conceptual framework on which to hang your thought processes in understanding what is happening within the eye.

Partial-thickness vitreous detachment traditionally has been called vitreoschisis, which is typically seen in complex diabetic pathology such as a diabetic tractional detachment. Vitreoschisis, however, is a more common occurrence than previously thought.

Partial thickness vitreous detachment may lead to epiretinal membranes (ERMs), which in the setting of centrifugal traction may lead to macular hole or macular pucker. Figure 1 shows the relationship of anomalous PVD to several retinal disorders.

What are our options for macular holes? For stage 1 macular holes, the most common strategy is watchful waiting because many of these will resolve. Once it becomes a full-thickness macular hole, spontaneous closure is uncommon, and if the patient is sufficiently symptomatic, surgical intervention, which will be discussed in an article beginning on page 8, is appropriate.

**VMA + VMT: NATURAL HISTORY**

The majority of patients with VMA and vitreomacular traction (VMT) present with cystoid changes in the macula. Microscopically, small cysts may be present,
which are easier to visualize with spectral-domain OCT (SD-OCT). Hikichi et al.\(^1\) showed that 81% of patients in their study presented with cystoid changes in the retina at the time of diagnosis of VMT; only 19% had no cystoid changes at the time of diagnosis. Over a median of 60 months, more than 90% of those with cystoid changes experienced severe vision loss, persistent cystoid changes, or development of new cystoid changes. In terms of visual acuity, 64% of the patients in this study lost more than 2 lines of vision, and 32% lost more than 6 lines of vision at 60 months.

The experience in this study with the natural history of VMT leads us to believe that the watch-and-wait approach may not be the best for many of our patients.

**CASE EXAMPLES**

Figure 2 shows the fluorescein angiography and corresponding OCT image of an eye of a patient with dry age-related macular degeneration. Macular changes and an attachment of the vitreous to the central macula can be seen, but there is no elevation of the macula and no visible cystoid changes. This is the type of case I see often on referral. Although there is a persistent VMA, I can see no traction and the patient's vision is 20/40, so I will not jump the gun with surgery.

Figure 3, however, shows a different case. This patient has a classic VMT, and the tractional effects are visible. Some ERM is present, and there are chronic cystoid changes to the retina. We know from experience that a case like this is unlikely to resolve, so if the patient is symptomatic and is bothered the visual distortion, I then intervene. In the past, I have performed surgery, but this is a perfect case for a medical intervention with a pharmacolytic agent if it were available.

There is nothing wrong with waiting, and there was a time when we would wait until the visual acuity was 20/70 or worse. Patients’ expectations, however, have changed, and they tend to be less tolerant of metamorphopsia than in years past. This is an important point. I am hesitant to operate on a patient who does not necessarily appreciate that they have a problem because he or she may very well notice the symptoms after I have operated and misinterpret them to be a result of the surgical procedure.

**SUMMARY**

Watchful waiting remains a reasonable approach to some cases of asymptomatic VMA; however, increased patient expectations have created a situation in which having a pharmacologic solution that can address visual symptoms without the risks of surgical intervention would be advantageous. The surgical approach to VMA and the associated risks will be discussed by Timothy G. Murray, MD, MBA, FACS, in the next article in this supplement.

David F. Williams, MD, MBA, is in private practice at VitreoRetinal Surgery PA in the Twin Cities of Minnesota, and is an Assistant Clinical Professor of Ophthalmology at the University of Minnesota.

The Surgical Approach to Vitreomacular Traction Syndrome

Advanced imaging and the use of intraoperative steroids can improve outcomes.

BY TIMOTHY G. MURRAY, MD, MBA, FACS

David F. Williams, MD, MBA, discussed the watch-and-wait approach to vitreomacular adhesion and macular hole and the fact that with stage 1 macular hole, there is up to a 50% rate of spontaneous resolution. What about our patients, however, who may require surgical intervention?

We do not currently have a uniform approach to surgery for vitreomacular traction (VMT) syndrome with or without macular hole, nor for epiretinal membrane (ERM). In my opinion, it is advantageous to release the ERM tractional component by removing the internal limiting membrane (ILM). There are data showing how altered anatomy via ILM removal results in a significantly lower incidence of recurrent ERM, persistent traction, or recurrent macular hole.1-3 Ten years ago, I do not think that ILM removal would be considered in the setting of standard surgical ERM management.

I also advocate the use of intravitreal steroids in vitrectomy, not for staining of the vitreous, but for their direct pharmacologic properties. It is true that there has been controversy regarding the occurrence of secondary sequelae, such as glaucoma or cataract formation, but we have performed ongoing evaluations at Bascom Palmer Eye Institute with intravitreal steroids used during surgery and there is strong evidence to support that they modulate macular thickening particularly in the immediate postoperative period with minimal risk of secondary glaucoma.4

COMBINED PHACO/VITRECTOMY CASE

A man aged 66 years was referred to the Bascom Palmer Eye Institute Corneal Service by an outside physician. He presented with 20/200 vision that was disproportionate to his cataract. A brief look at the macula revealed dense ERM and VMT with metamorphopsia (Figure 1). The fellow eye had some drusen (Figure 2).
but no other significant pathology.

In this setting, I am a proponent of combining cataract and vitrectomy surgery as vitrectomy alone would not recover best visual acuity and the patient would have to undergo cataract surgery at a later date to ensure the best visual acuity. Combined pars plana vitrectomy and phacoemulsification surgery is the norm for patients managed outside of the United States with retinal pathology requiring surgical intervention and concomitant significant lens opacity. These combined procedures are much less commonly performed in the United States but appear to be increasing in frequency with the shift to microincisional vitrectomy surgery and clear cornea torsional phacoemulsification.

In this case, first I made the sclerotomies, and inserted valved trocars (Alcon Laboratories Inc.) to stabilize the fluidics. I performed torsional phaco through a clear corneal wound and implanted a foldable intraocular lens, leaving the viscoelastic in the eye. I proceeded to core vitrectomy, peeling the hyaloid membrane by engaging it with the vitrector. I prefer to remove the hyaloid anterior to the equator but not all the way to the ora serrata. Using indocyanine green (ICG) as a staining agent, I peeled the ERM and the ILM. I peel the ERM first, because it is difficult to engage the ILM over the ERM.

Staining agents have revolutionized my approach to membrane peeling. When I was in training, the theory was that when you peeled the ERM, you never went back and peeled the ILM because intraretinal edema and striae from the ERM peel compromised visibility.

With ICG, however, I can easily identify residual ILM and am able to engage the tissue for removal.

One week after surgery, some traumatic impact sites remain from the peel but the membrane is gone and the contour has improved. Eight months later, he is pseudophakic, his metamorphopsia has decreased, and his vision has improved to 20/30 (Figure 3), but he is incredibly unhappy. Why?

The reason for his dissatisfaction is that he continues to have some persistent metamorphopsia. One thing that I am seeing more frequently in my practice is that now that we have the ability to significantly improve visual acuity, patients are more focused on quality of vision, almost as they would with refractive surgery. I typically tell my patients to expect a 2/3-line improvement in visual acuity in a case such as that I have described. So in this case, I advised the patient that he would most likely be 20/50 after surgery and his vision is even better at 20/30. I am thrilled. He is unhappy. This is, in my opinion, a result of increased patient expectations and is simply a consequence of our success in managing patients’ disease.

CONSIDERATIONS IN SURGERY FOR VMT

The complications that are associated with surgery for VMT include a potentially higher incidence of retinal breaks, both intraoperatively and postoperatively, retinal detachments, and endophthalmitis.

Additionally, there is a possibility of incomplete separation of the vitreous, ERM, or ILM, with the potential for vasoactive and vasoproliferative substances affecting retinal function, the possibility for development of fibrovascular membranes, and iatrogenic trauma to the retina. The risk of complications is higher in more complex cases, so this must also be considered.

I am a strong believer in the use of a staining agent to facilitate ILM removal. It is also my experience that the use of adjunct intravitreal triamcinolone during vitrectomy can enhance resolution of intraretinal edema. Further, in my opinion, a combined approach when visually significant cataract is present is better than having the patient undergo 2 separate procedures, and it is critical to stabilize the anterior segment prior to

Figure 3. Postoperative imaging of the affected eye shows improvement. The patient was unhappy, however, because of residual metamorphopsia.
Symptomatic Vitreomacular Adhesion

Optical coherence tomography has helped improve our understanding of which patients with VMT will benefit from surgery.

Ocriplasmin for the Treatment of Symptomatic Vitreomacular Adhesion

Favorable phase 3 data on safety and efficacy prove the benefits of this pharmacologic option to induce posterior vitreous detachment.

BY CARL D. REGILLO, MD

The definition of pharmacologic vitreolysis is the intravitreal use of pharmacologic agents to cleave the vitreoretinal interface and alter the molecular organization and structure of the vitreous to reduce or eliminate its role in disease formation.1

The potential treatment benefits to pharmacologic vitreolysis include complete atraumatic posterior vitreous separation, creation of a more physiologic vitreomacular interface, prevention of fibrovascular proliferation, and prophylaxis or treatment of macular edema and exudation. As David F. Williams, MD, MBA, noted in his article, vitreomacular adhesion (VMA) is implicated in many different retinal disease states, including not only macular hole and macular pucker, but possibly also age-related macular degeneration, proliferative diabetic retinopathy and macular edema from diabetic retinopathy and retinal vein occlusion.

Table 1 shows the various agents that have been evaluated for vitreolysis. The evolution of understanding of how these pharmalytic agents work have led to ocriplasmin (ThromboGenics), the only agent that can produce both liquefaction and separation of the vitreous from the retina. Additionally, as seen in the Table, there is no toxicity associated with ocriplasmin, unlike many of the agents that have been investigated for vitreolysis. Lastly, it is the only agent to have successfully gone through phase 3 studies.

PRECLINICAL DATA

Ocriplasmin is manufactured with recombinant technology to target fibronectin, laminin, and collagen and cleanly separate the vitreous from the internal limiting membrane (ILM), inducing both liquefaction and vitreous detachment.2 The proof-of-concept studies of ocriplasmin in both postmortem human eyes and mouse eyes evaluated the enzymatic agent for its vitreolytic effect, its efficacy for inducing posterior vitreous detachment, and safety of its intravitreal injection. Figure 1A shows histological studies of a normal mouse eye and Figure 1B shows PVD induction after ocriplasmin injection. Not only did the vitreous separate from the retina surface, but there is less fibronectin and collagen within the vitreous body after ocriplasmin injection. The results of these preclinical studies confirmed the hypothesis that ocriplasmin is a potential pharmacologic therapy for vitreomacular adhesion (VMA).3

PHASE 3 DATA

The phase 3 studies for ocriplasmin, the MIVI-Trust program, randomized a total of 652 patients to either a single injection of 125 µg ocriplasmin (n=464) or placebo (n=188). The placebo group received an equal volume
### PHARMACOLOGIC VITREOLYSIS AGENTS

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<tr>
<th>Dispersed Proteases</th>
<th>Nattokinase</th>
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<tr>
<td><strong>Description</strong></td>
<td></td>
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<tr>
<td>• Neutral protease obtained from <em>Bacillus polymyxa</em></td>
<td>• Serine protease produced by <em>Bacillus subtilis</em></td>
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<tr>
<td>• Preferentially cleaves fibronectin and collagen</td>
<td>• Potent fibrinolytic activity, enhances plasminogen activators and inactivates a plasminogen-activator inhibitor</td>
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<tr>
<td><strong>Advantages</strong></td>
<td></td>
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<td>• Evidence of PVD induction in vitro and in vivo</td>
<td>• Demonstrated PVD in rabbits</td>
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<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
</tr>
<tr>
<td>• Recently showed evidence of retinal hemorrhages</td>
<td>• No human studies</td>
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<tr>
<td>• Breaches in the ILM</td>
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<td>• Epiretinal membrane</td>
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<td>• Reduction in baseline electroretinogram amplitude</td>
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<td>• Ultrastructural damage to the retina</td>
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<table>
<thead>
<tr>
<th>Hyaluronidase</th>
<th>Chondroitinase</th>
<th>Collagenase</th>
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<tr>
<td><strong>Description</strong></td>
<td>• Cleaves hyaluronan and collagen complex, resulting in liquefaction of the vitreous</td>
<td>• Maintains gel state of vitreous by bridging adjacent collagen fibrils</td>
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<td><strong>Advantages</strong></td>
<td>• Has potential to increase diffusion rate of erythrocytes and facilitate their clearance by lysis and phagocytosis</td>
<td>• Reported to induce PVD without damage to ILM, detach epiretinal membranes, and facilitate vitreous removal</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Sufficient clearance of hemorrhage not demonstrated in Phase III (Vitrase, Ista)</td>
<td>• No reports of its use on human eyes published.</td>
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injection of saline, which negated any volumetric effect on vitreous separation and confirmed that the difference between the 2 arms was indeed a drug effect.

The primary endpoint of the studies was pharmacologic resolution of VMA at day 28. Secondary endpoints included total PVD at day 28, nonsurgical closure of full-thickness macular holes, change in visual acuity, the need for a vitrectomy procedure, and responses on a visual function questionnaire.

Patients were required to be symptomatic. It is important to note that patients with very good baseline visual acuity were allowed into this study, ≤20/25, because this could result in a ceiling effect with regard to visual acuity gains. Additionally, patients with epiretinal membrane could be included in the study. Patients with high myopia (>8 D), prior vitrectomy or laser, macular holes >400 µm, and other retinal diseases that could affect visual function were excluded.

The trials were comprised of 3 different “buckets” of patients: those with macular hole (as noted, they could also have had ERM as well, and 23 patients had baseline macular hole and ERM); patients with ERM (baseline ERM, no baseline macular hole; it is important to note that ERM was not being treated, but that VMA associated with ERM was being treated); and vitreomacular traction (VMT) syndrome (with no baseline macular hole or ERM). All patients were required to have VMA confirmed by a central reading center (Duke Reading Center).

The proportion of patients who had VMA resolution at day 28 was 29.8% vs 7.7% in the active treatment group vs placebo group, respectively. If you take the extent of adhesion into account, the resolution rates in the ocriplasmin group were even higher in eyes with smaller areas of adhesion (≤1500 µm), approaching 34% in patients with smaller adhesions as opposed to broader adhesions. Optical coherence tomography (OCT) imaging demonstrates that smaller adhesions were more easily resolved at day 28 (Figure 2).

In terms of visual acuity outcomes, approximately 41% of ocriplasmin-treated VMT patients who achieved VMA resolution gained 2 or more lines at 6 months, which was from a good baseline visual acuity approaching nearly 68 letters (20/50).

The mean visual acuity gain was 7.3 letters in ocriplasmin-treated VMT patients who achieved VMA resolution. This is significant considering the good baseline visual acuity of these patients. Seven patients lost vision. Patient 1: -1 letter (73 ≥72). VMA resolution by day 7. Also had cystoid macular dystrophy in study eye. Patient 2: -2 letters (74 ≥72). VMA resolution by day 28. Patient also had drusen, cataract and dry AMD in study eye. Patient 3: -2 letters (73 ≥71). VMA resolution by D7; myopia in study eye. Patient 4: -2 letters (83 ≥81). VMA resolution by day 7. Patient also had dry eye and cataract in study eye. Patient 5: -5 letters (60 ≥55). VMA resolution by day 14. Patient also had drusen and dry AMD in study eye. Patient 6: -6 letters (72 ≥66). VMA resolution by day 7. Patient initially lost 12 letters and was recovering vision when lost to follow-up (3 months). Patient 7: -11 letters (53 ≥42). VMA resolution by day 7. Patient also had a cataract in the study eye.

MACULAR HOLE SUBGROUP ANALYSIS

The differences between ocriplasmin and placebo groups were even more pronounced in patients who were included in the macular hole subgroup. These patients were required to have stage 2 full-thickness macular holes, such as these seen on OCT in Figure 4.

In this subgroup, 40% of full-thickness macular holes closed with a single injection of ocriplasmin. These holes closed early (by day 28) and remained closed at month 6.

Smaller macular holes (≤250 um) closed at a much higher rate than did larger holes (>250 um). Again, these holes closed early and remained closed.

In terms of visual acuity, 77% of patients gained 2 or more lines with hole closure at 6 months after a single
Injection of ocriplasmin, which was to be expected considering the patients’ mean baseline visual acuity (54.8 letters, 20/80). It is important to note that vision gains occurred over time, demonstrating that, as is the case with surgery, the drug works quickly to close the macular holes, but the improvement in visual acuity is gradual.

The mean visual acuity gain was 14.1 letters in ocriplasmin-treated macular hole patients who achieved hole closure with drug treatment only. Only 1 patient in this subgroup lost vision. This patient’s macular hole (387 µm) closed at day 7 and the eye lost 1 letter of vision (74 to ≥73 letters). The patient also had pterygium, cortical cataract, cupping of the optic disc, retinal pigment epithelial changes, vascular narrowing, and macular edema in the study eye at diagnosis.

Figure 5 shows the closing of a macular hole and resolution of VMA in a patient in the macular hole subgroup after a single injection of ocriplasmin.

The rate of macular closure with placebo alone was 17%, as compared to 40.6% in patients with ocriplasmin alone. For patients who received placebo or ocriplasmin and did not have full-thickness macular hole closure and went on to have a vitrectomy, the rates of closure were 92.3% for the placebo group vs 93.1% for the ocriplasmin group, demonstrating that ocriplasmin did not affect the ability to close a macular hole with vitrectomy.

**SAFETY DATA**

Because many of patients who have the potential to benefit from ocriplasmin are among those who we would watch and wait and not perform surgery, the safety data are critical. From day 0 to day 7 after injection, there were a small number of incidences of floaters, eye pain, photopsia, blurred vision, reduced visual acuity, visual impairment, retinal and macular edema, anterior chamber cell flare, and photophobia in the patients who received ocriplasmin as compared to the lower number or no incidences in the patients who received placebo injection. Beyond 7 days out to 6 months, most of these side effects drop off to where there is little to no difference between the groups.

Because of these data, it is apparent that ocriplasmin injection can cause temporary visual acuity changes, and this is why it is important to counsel patients so that they are aware of this transient effect.

In terms of more serious side effects associated with induced PVD, such as retinal tears and detachment, the rates were actually lower in the ocriplasmin group than with placebo.

**SUMMARY**

These data show that a single injection of ocriplasmin results in increased rates of PVD and full-thickness macular hole resolution. Resolution of VMA and macular hole resulted in visual improvement in most patients, and most of the adverse events were transient and occurred in the immediate week following injection.

Further, ocriplasmin did not preclude future vitrectomy if the drug did not result in macular hole closure. Should ocriplasmin become available, pharmacovitreolysis will offer physicians an attractive alternative for our patients who have symptomatic VMA.

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1. The best-case scenario for posterior vitreous detachment (PVD) includes which biologic phase(s)?
   a. liquefaction
   b. A and C in synchrony
   c. separation of the vitreous from the retina
   d. synesis

2. Hyaluronidase achieves interface separation without liquefaction; Dispase causes liquefaction.
   a. true
   b. false

3. Which complications are associated with surgery to induce PVD?
   a. retinal detachment
   b. lid disease
   c. endophthalmitis
   d. A and C

4. Vitreomacular adhesion (VMA) has been implicated in the following disease states:
   a. diabetic retinopathy
   b. age-related macular degeneration
   c. uveitis
   d. A and B
   e. A and C

5. Ocriplasmin is manufactured with recombinant technology to target _______.
   a. collagen
   b. VEGF
   c. fibronectin
   d. edema
   e. B and D
   f. A and C

6. What is a reasonable approach for a patients with dry age-related macular degeneration who presents with the following: macular changes on optical coherence tomography, visible attachment of the vitreous, no visible cystoid changes, and relatively good visual acuity of 20/40?
   a. surgery
   b. watch and wait
   c. intravitreal injection of anti-VEGF
   d. none of the above

7. Ocriplasmin can cause temporary visual acuity changes.
   a. true
   b. false
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