CME ACTIVITY

The Evolving Management of Vitreomacular Interface Disorders: When To Treat

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GAP ANALYSIS

With improved imaging technologies and new treatment options, the prominence of symptomatic vitreomacular adhesion (VMA) in clinical practice has increased and patient care has been impacted. As a result, a gap may exist between existing clinical evidence and clinical practice if retinal specialists are not current in their management of symptomatic VMA. For optimal patient care, practitioners need to be knowledgeable of all treatment options and their implementation into practice.

Because patient populations in clinical practice often differ from those in clinical studies, outcomes may differ as well. For optimal patient outcomes in real-world settings when implementing new treatment strategies, practitioners need to be aware of patient selection criteria and predictors of treatment response; they must also be informed of potential adverse events and their management; and know how to counsel patients and set appropriate patient expectations.

Gap 1: Because of recent advances, retina specialists may not be current in their knowledge of the role of symptomatic VMA in retinal diseases.

Gap 2: Retina specialists may not have access to the data needed to translate clinical trial results into clinical practice, including proper patient selection, expected outcomes, potential risks, and patient counseling strategies. There is no easily accessible resource available that contains the latest information presented on treatment options for symptomatic VMA.

Gap 3: Retina specialists may not have sufficient experience with new therapies and need guidance on their use in real-world settings.

STATEMENT OF NEED

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 posterior vitreous detachment (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.

Symptomatic VMA 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 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 VMT 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 vary5-12 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 complications. Clinical studies with standard PPV12-15 and more recently with small-gauge PPVs16-20 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 nusus 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 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 for earlier intervention, whereas surgery is reserved for more advanced cases. In 2 phase 3 studies, a single injection of ocriplasmin (Jetrea, Thrombogenics) was shown to be safe and effective for PVD induction,23 providing further evidence that pharmacologic vitreolysis with ocriplasmin may provide an safe and effective alternative to PPV for inducing PVD. Further, the largest-ever retrospective review of patients with VMA, VMT, and macular hole (n = 509) conducted to date suggested that early treatment initiation with ocriplasmin may stop disease progression and lead to better visual function outcome.24

LEARNING OBJECTIVES
Upon completion of this activity, participants should be able to:
• Explain the pathogenesis of VMA and its role in various retinal pathologies
• Identify the benefits of induced PVD vs anomalous PVD
• Discuss the available data on both surgical and pharmacologic PVD induction
• Differentiate between the various vitreolysis agents for PVD induction and their safety and efficacy profiles

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Diagnosis and Management of Vitreoretinal Interface Disorders

BY CARL D. REGILLO, MD, FACS

Our understanding of the vitreoretinal interface and ability to treat pathology in this location has improved dramatically with the advent of ocular coherence tomography (OCT). Because this is still a somewhat new area of knowledge, there is often incomplete knowledge combined with conflicting vocabulary used to describe disorders of the vitreoretinal interface. Having a consistent understanding and terminology will help us advance in our ability to treat these disorders.

DEFINING THE DISORDERS

Vitreoretinal or vitreomacular adhesion (VMA) may represent either normal or pathologic posterior vitreous detachment in evolution. It is usually an incidental finding on OCT examination as VMA alone does not cause any retinal distortion, nor should you find other symptoms (Figure 1).

Vitreomacular traction (VMT) is when this area of attachment is causing neurosensory retinal distortion. Epiretinal membrane may or may not be present, and it is associated with a broad spectrum of diseases. VMT’s natural history and outcomes vary greatly (Figure 2).

The third disorder of the vitreoretinal interface is full-thickness macular hole (FTMH). This is often found with surrounding edema and VMA may or may not be detected as well (Figure 3).

TREATING VMA AND VMT

With all of these pathologies, there can be broad or focal attachments, mild or severe traction, and holes of varying sizes; but the historic treatment options all basically come down to observation or vitrectomy surgery. For asymptomatic VMA, waiting and watching is a straightforward decision. But once there is traction that is causing visual symptoms, there are several factors to consider.

Conventional wisdom considers doing nothing to be the least risky action. But if delayed intervention leads to greater visual loss, then waiting also has a certain risk. A big factor in the difficulty of evaluating treatment options is the ambiguity in the published literature. Among the small number of studies published, some were performed prior to OCT, limiting the ability to actually see the impact of therapy. Other studies were small, had short-term follow-up, or were nonrandomized. This hardly contributes to an irrefutable body of evidence.

The following three studies are among the more prominent when seeking information on disorders of the vitreoretinal interface. Hikichi and colleagues followed 53 patients with VMT for a median of 60 months, but this was prior to OCT, so our understanding of the pathologic changes is limited. However, combining the 43 patients with cystoid changes and the 10 with milder disease without cystoid changes at baseline, only 11% achieved spontaneous posterior detachment. In contrast, 64% manifested a decrease in visual acuity of 2 or more lines. This is a very poor natural history.

A newer study by Odrobina and colleagues included only 19 patients with VMT for an average of 8 months of follow-up, but overall showed similar results to the Hikichi study. While 47% of patients achieved spontaneous posterior vitreous separation, 89% (n = 17) had some persistent retinal abnormalities identified by OCT.

The most recently published study by John and colleagues followed 106 eyes of 81 patients with VMT for a median of 23 months. The investigators found that 32% of patients achieved spontaneous release. However, again, 67% either had stable or worsening cystoid changes present on OCT.

With a range of 11% to 47% of patients achieving spontaneous detachment, a time lapse varying from
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8 to 15 months for spontaneous resolution, and 64% to 89% of eyes showing persistent cystoid changes, VMT becomes a very difficult pathology for which to determine the optimal timing of treatment.

FTMH

Macular holes, on the other hand, are easier to categorize, and treatment appears to have better outcomes. We know that once there is a FTMH, it will progress and vision will continue to decline in most cases. Even with a small, stage 2 FTMH, 75% or more progress to larger holes, resulting in a decline of visual acuity. Spontaneous closure is rare, with a real-life rate probably closer to 3% rather than the optimistic 11% that has been published in the past. It is also important to consider that intervention when the hole is less than 6 months in duration yields better anatomical and functional results.

With the current techniques in vitreoretinal surgery, closure rates are well over 90% and most patients do have visual improvement. Potential side effects of vitrectomy surgery include progression of cataract, retinal tears, and retinal detachment. Traditionally, vitrectomy was the primary treatment modality. However, we now have a pharmacologic option for selected cases of VMT and FTMH that is effective, works quickly, and does not impact the potential for vitrectomy surgery in the future. It is important to learn how and with what patients this new pharmacologic option is best used.

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Figure 3. A full-thickness macular hole without the presence of VMA.
Pharmacologic Vitreolysis: Current Management of Vitreo-Interface Disorders

By Allen C. Ho, MD

Many patients with symptomatic vitreomacular adhesion (VMA) may be candidates for a pharmacologic treatment option. This option allows for the resolution of the underlying VMA while possibly avoiding the risks and inconvenience of surgery. For patients who do receive this pharmacologic intervention, surgery remains an option if the adhesion is not released.

One such treatment, ocriplasmin (Jetrea, ThromboGenics), has been tested in a variety of clinical trials over the last decade. It is manufactured by recombinant DNA technology and targets fibronectin, laminin, and collagen in the vitreous body and vitreoretinal interface (Figure 1). Administered by an intravitreal injection, it induces liquefaction at the vitreoretinal interface. At 27 KD, it is a relatively small molecule compared to others that we inject in the eye.

**PHASE 3 MIVI–TRUST CLINICAL TRIAL RESULTS**

The pivotal Phase 3 MIVI-TRUST clinical trials2,3 led to the approval of ocriplasmin for VMA, both in Europe and more recently in the United States. Two multicenter, randomized, double-blind, placebo-controlled studies were conducted to test a single intravitreal injection of ocriplasmin. The study design ratio of randomized assignments of the MIVI-TRUST MIVI-006 trial in the United States was 2:1, and for the MIVI-007 trial in Europe and the United States, the ratio was 3:1. The primary endpoint was resolution of VMA at day 28. Patients were then followed to month 3 and month 6 for safety and further efficacy.

**Inclusion/Exclusion**

Key inclusion criteria included patients 18 years or older with symptomatic VMA, with symptoms attributable to this adhesion as determined by the investigator. The best corrected visual acuity had to be 20/25 or worse in the study eye and 20/800 or better in the non-study eye. Key exclusion criteria included high myopia greater than 8.0 D, a history of prior vitrectomy or prior laser photocoagulation in the macula, and those with larger macular holes, 400 µm or greater, although some were included. Overall, 652 eyes were included. Patient demographics and baseline disease characteristics were similar in both groups, although there were more pseudophakic (37.1% vs 28.2%) patients and more female patients (67.7% vs 61.2%) in the ocriplasmin group. Patients were randomly assigned a single 100-µL intravitreal injection containing 125 µg ocriplasmin, or a placebo intravitreal injection of 100 µL saline. It is significant to note that this was an actual fluid injection in the placebo group.

**Efficacy**

The trials resulted in a rate of release at day 28 of 26.5% in ocriplasmin versus 10.1% in the placebo group, (P < .001)—this was the foundation for the efficacy approval of ocriplasmin for VMA.4 Of the patients who achieved a release after receiving an injection of ocriplasmin, 80% released within the first 14 days.

Looking at the specific group of patients with full thickness macular holes who resolved by day 28 by treatment group, the between group differences are even greater than with the VMA patients. In the ocriplasmin group, 40% of macular holes resolved by day 28 compared with 10% in placebo group (Figure 2).

Looking at time to full thickness macular hole closure in eyes with VMA, 70% of those macular holes expected to close by day 28 closed within 1 week, and 80% closed by 2 weeks (Figure 3). This is similar to what was seen with the overall group of VMA. Whether there is a macular hole or just vitreomacular traction, most of the patients will resolve within the first 1 to 2 weeks.

Those patients with smaller holes less than or equal to 250 µm have a closure rate of almost 60%, while those with holes between 250 to 400 µm achieve a closure rate of about 37%. There were 22 patients who were enrolled with macular holes greater than 400 µm; among these eyes enrolled in the study outside of the inclusion criteria, none of the holes greater than 400 µm resolved.

Overall, looking at all holes less than or equal to 400 µm, 50% of macular holes resolved with ocriplasmin.

**Safety**

Safety is a concern with any therapy, and overall, in my experience, ocriplasmin has been a safe drug to date. However, patients should be aware that ocriplasmin has been associated with an increase in floaters, photopsias or blurred vision, and occasional retinal edema. However, by the second week of the MIVI-TRUST trials, rates of ocular adverse events become very similar between the placebo and Ocriplasmin groups.

There were also reports of visual acuity loss in
MIVI-TRUST. Overall, between the ocriplasmin and placebo groups, 1.6% of patients had a 2 or more line decrease in visual acuity within the first week; by 6 months, the rate was 1.1%. There was a decrease of 2 or more lines within the first week in 7.7% of patients in the ocriplasmin grous, but by month 6, that rate improved to 1.3%. Reasons for the decrease in vision in the study were VMA resolution with transient subfoveal fluid, progression of the macular hole, or progression of the vitreomacular traction. This is significant and should be included in the risks and benefits discussions with patients being considered for ocriplasmin.

Electroretinographies (ERGs) were performed in the small number of patients who had significant loss of vision after an injection. Of the 10 cases reported in the biologics application, 6 of the cases resolved and there was a spectrum of ERG abnormalities observed including mild decreases in A and B wave amplitude to isoelectric responses. This is something that needs to be studied more carefully. A more systemic ERG sub-study is being done in the fully recruited, ongoing OASIS study.

With respect to retinal tears and detachments, there was no significant difference between ocriplasmin and placebo before vitrectomy. Some patients did not release and went on to vitrectomy. The rates for any retinal tear or detachment were 14% in the placebo group and 8.5% for the ocriplasmin group. Similarly, with respect to cataract progression, there were no differences between placebo and ocriplasmin before any consideration of vitrectomy or subsequent to the vitrectomy.

One of the issues for lenses and cataract surgery is whether or not patients will have unstable lenses during subsequent cataract surgery because the enzyme may act on the zonules. In the MIVI-TRUST-007 trial, there was one patient with lens instability. Looking at all the MIVI ocriplasmin trials, there was another patient in MIVI-009 who had lens subluxation. This is something that needs further study and something that we need to look at in the postmarketing safety.

**POSTMARKETING ADVERSE EVENTS SUMMARY**

In addition to the decrease in visual acuity and the cases on ERG change already discussed, the incidence of dyschromatopsia or yellow vision (Figure 4), black and white vision, or impaired color vision in the clinical trials was about 1% to 1.5%, and less than 1% in the postmarketing experience. Regarding new or worsening macular holes, the results were 6.7% in the clinical trials, with less than 1% in postmarketing experience. The rate of new or worsening macular holes in the inner/outer segment (IS/OS) junction or the ellipsoid zone on optical coherence tomography (OCT) was 0.2% in the postmarketing analysis. One study noted transient outer segment ellipsoid zone loss in 7 patients and
subretinal fluid presence following injection in 5 patients.

Macular holes, and specifically smaller macular holes, may release on the order of 50% to 60% of the time with ocriplasmin. Patients who do receive ocriplasmin and release and develop subfoveal fluid will have transient visual loss. Some of the cases that have been seen post marketing have persisted and have had significant visual loss so we look forward to more follow-up there. We also look forward to more follow-up regarding lens stability and certainly with respect to the ERG findings that have been observed rarely, but have been dramatic.

FUTURE STUDIES

Looking to the future, we are anticipating the results of the OASIS trial in which 120 patients were enrolled and will be followed for 24 months. We are looking for better safety information, better ellipsoid zone analysis, and information on a subset of patients who will be getting full-field ERGs over the course of the study. A registry trial called the ORBIT study will be including 120 centers with over 1500 patients and 12 months of follow-up to provide more information on real world safety and efficacy for ocriplasmin (Figure 6).

CONCLUSION

In the clinical trials, ocriplasmin was effective in about 27% of cases for inducing a release of symptomatic vitreomacular adhesion. Release typically occurred within 1 to 2 weeks, and then the frequency of release decreased approaching the 1 month timepoint. It should be noted that in those patients in whom a pharmacologic release is not achieved, that surgery is still a viable option.

What has resonated with me as a user of ocriplasmin over the past year is the efficacy and safety in light of and in comparison to surgery. There are associated risks; transient vision loss occurs in about 7% of cases, but the rate of persistent vision loss is less than 1%. This is comparable to surgical correction of symptomatic vitreomacular traction.

The efficacy of pharmacologic vitreolysis is also similar to surgery, in that ocriplasmin is not a magic bullet and patients will not get better right away. Patients should be counseled that they may get a little worse before they get better.

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Does Patient Selection Influence Outcomes in the Use of Pharmacologic Vitreolysis in Treating VMT and Macular Hole?

BY SUNIR J. GARG, MD

Historically, a diagnosis of vitreomacular traction (VMT) left patients with few treatment options: sit and wait, or in severe cases, proceed to surgery. Enter pharmacologic vitreolysis, a relatively new treatment option which uses ocriplasmin (Jetrea, Thrombogenics, Inc.), an enzyme administered via intravitreal injection that breaks down proteins in the eye responsible for VMT. Multiple studies demonstrate resolution of VMT using the intravitreal injections with top line data from the ocriplasmin phase 3 Microplasmin for IntraVitreous Injection Traction Release without Surgical Treatment (MIVI-TRUST) clinical trial program indicating a 62% increase in release. Although the results were quite impressive, there may be further improvement with results by selecting patients who have specific clinical features (Figure 1).

THE STUDY

The MIVI-TRUST Study Group set out to identify baseline features predictive of pharmacologic resolution of VMT at day 28 following a single intravitreal injection of ocriplasmin. Data was analyzed for 652 subjects (652 eyes) included in the MIVI-TRUST clinical trial program. Multivariate regression analysis was used to identify independent baseline features associated with pharmacologic resolution of VMT, and the findings were divided into 2 subgroups: those with VMT and those with macular hole.

VITREOMACULAR ADHESION SUBGROUP

Age

There was an impressive trend towards younger patients having a much higher release rate compared to older patients. Patients older than 74 years had approximately a 14% release of vitreomacular adhesion (VMA) compared with 3% in placebo; but in patients younger than 65 years, nearly 50% of patients had release compared with less than 25% with placebo (Figure 2).

Multiple factors may contribute to this finding. The most likely reason is that as the patients got older, they were more likely to have already release of the hyaloid and release of VMA, so older patients who had VMA at the time of enrollment likely had more “sticky vitreous” than patients who were not enrolled in the trial.

Macular Hole

The presence of a macular hole at baseline also seemed to affect outcomes. Patients who did not have a macular hole at baseline had approximately 20% release with ocriplasmin, but that improved to 50% of patients if they had a full thickness macular hole at baseline.

VMA

The width of the VMA also considerably affected success rates. Approximately 6% of patients with a broader area of vitreomacular adhesion greater than 1500 µm had release with ocriplasmin; however, the results were significantly better with an approximate 35% release rate in patients with an area of adhesion less than 1500 µm.

Epiretinal Membrane

Presence of an epiretinal membrane reduced success. Less than 10% of patients who had an epiretinal membrane at baseline experienced release with an ocriplasmin injection. This improved to 37% of patients when no epiretinal membrane was present at baseline.
Lens Status

Compared with phakic patients, pseudophakic patients tended to have a much lower rate of VMA release with ocriplasmin. While it is not exactly clear why this occurs, pseudophakic patients are more likely to develop a posterior vitreous detachment (PVD) in the months following cataract surgery. Perhaps patients who had cataract surgery, but who did not develop a PVD or spontaneously released their VMA, potentially had a more “sticky” hyaloid, and, therefore, were less likely to respond to pharmacologic therapy.

Summation of Vitreomacular Adhesion Subgroup Data

Younger patients and those with macular holes tend to have results nearly twice as good as the top line data in the MIVI-TRUST trial. Patients without epiretinal membrane, those with VMA diameter of less than 1500 µm, and phakic patients also tended to have much better results. Additionally, if patients have 2 positive predictive factors, the results are even more impressive. A young patient without an epiretinal membrane or a young patient with a vitreomacular adhesion of less than 1500 µm has a nearly 60% VMA release rate with an ocriplasmin injection (Figure 3).5

Macular Hole Subgroup Analysis

In a subgroup of patients with a macular hole, multivariate regression analysis was used to identify baseline features predictive of pharmacologic full-thickness macular hole closure at month 6 following a single intravitreal injection of ocriplasmin. Data from patients who had vitreomacular traction as well as a coexisting full-thickness macular hole were examined. The study included 153 eyes with baseline full-thickness macular holes; 106 in the ocriplasmin arm and 47 in the placebo arm.

Patients who had smaller macular holes experienced a much higher closure rate than those with larger macular holes. If a patient’s macular hole was less than 250 µm in diameter, there was a nearly 60% closure rate with a single ocriplasmin injection. The closure rate was still quite high at approximately 37% in patients who had macular holes greater than 400 µm in size.
holes between 250 and 400 µm in diameter; however, none of the patients who had macular holes larger than 400 µm in diameter closed. From this, we can safely conclude that patients in this category would not be good candidates for ocriplasmin. When combining the smaller diameter subgroups, approximately 50% of patients with macular holes less than 400 µm in diameter had closure (Figure 4).

CONCLUSION
Baseline features do seem to influence VMA resolution. The best results appeared among patients younger than 65 years of age, patients who have no evidence of an epiretinal membrane, and patients who have vitreomacular adhesion of less than 1500 µm. Lens status is also a factor with phakic patients experiencing higher success rates compared to pseudophakic patients. In terms of macular hole closure, patients with macular holes less than 400 µm in size have much higher rates of closure compared to larger holes. Patient selection based on key positive predictive parameters yields high success rates for pharmacologic intervention.

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As with any new therapy, it is important to adequately analyze the safety data to properly assess the risk profile. The safety data for ocriplasmin (Jetrea, ThromboGenics) comes from the MIVI-TRUST clinical trials, and presents the more common early and late side effects that can be encountered with patients who receive the injection.

COMMON SIDE EFFECTS

The most common side effects associated with ocriplasmin are vitreous floaters, eye pain, photopsia, and blurred vision (Figure 1). These are not surprising side effects, as the enzymes in ocriplasmin are designed to digest the vitreous in a rapid fashion, creating floaters, flashes, and photopsia in a more intense manner than with spontaneous posterior vitreous detachment (PVD). Blurred vision also coincides with the digestion of the vitreous and is usually transient.

Eye pain is usually transient and more associated with the injection itself. Most injections in the United States are performed under topical anesthesia using iodine, and the iodine is the most likely cause of the eye pain encountered following an injection.

More unusual side effects include retina edema, macular edema, and inflammation. The presence of subretinal fluid, interestingly, has been seen after vitreomacular traction release, both spontaneous and pharmacologically induced. Thus, it is probably related to the release itself rather than an effect of the drug. While the mechanism is still not know, we speculate that it is possibly the result of increasing physical traction before the release. It was previously considered that subretinal fluid developed only with full release, but it has been discovered when there is still a partial attachment. When this subretinal fluid does develop, it spontaneously resolves over several months (Figure 2).

Ellipsoid zone changes on OCT are associated with the release of vitreomacular traction (VMT). Thus far, these changes are only seen when ocriplasmin has been used and release has occurred, but they are not seen in every case of ocriplasmin-induced release. Occasionally, these ellipsoid zone changes are accompanied by a decrease in visual acuity, and both usually resolve between 2 and 6 months. This suggests a drug effect and preliminary thoughts are that this could be due to the ocriplasmin actually partially digesting the interphotoreceptor matrix, resulting in the transient decrease in vision.

The release is thought to possibly allow the drug increased access to the subretinal space, as the ellipsoid changes and decrease of visual acuity only occur with release. However, there is no firm data to confirm these hypotheses. If you follow these patients, the changes to the ellipsoid zone resolves and there is reconstitution to a healthy, normal appearance.

Retinal tears or detachments are occurring less than 3% of the time in the ocriplasmin group and higher than that in the placebo group. As some of the patients treated with ocriplasmin achieved PVD without requiring vitrectomy, it is presumed that the vitrectomy itself is associated with a small risk of vitreoretinal tear or detachment. This would explain why patients in the

- **Safety Data: Day 8 – End of Study (Month 6)**

- **Mechanism of subretinal fluid accumulation**

- **Subretinal fluid developed prior to complete release**

Figure 1. Summary of safety data in the MIVI-TRUST clinical trials.

Figure 2. Accumulation of subretinal fluid after ocriplasmin injection.
placebo group have a higher risk of these complications, as they have an increased incidence of vitrectomy.

**TRANSIENT SIDE EFFECTS**

All of the most common side effects are seen in the first week following injection of ocriplasmin, and by the second week and to the end of the study, most or all of these have diminished. The floaters diminish and become more comparable with placebo, and the eye pain and photopsia diminish. The blurred vision or reduced vision decreases and even the rare retinal edema is also diminished. Most of these effects can be expected to decrease by three months and definitely by 6 months.

While clinical scenarios can vary, an average patient with 20/50 vision at baseline can be expected to drop to 20/200 following the injection. However, they can achieve release of the VMT and improve to 20/32 two weeks later (Figure 3).

**CASE STUDY I**

A 72 year-old male had a full-thickness macular hole (FTMH) with focal VMT in his left eye, with visual acuity of 20/200. He underwent an injection of ocriplasmin, and 7 days post injection, there was release of the VMT. However, the macular hole remained full thickness and his visual acuity further declined to 20/400. He subsequently underwent pars plana vitrectomy with internal limiting membrane peel and had successful closure of the macular hole. His vision stabilized at 20/60.

**CASE STUDY II**

A 63 year-old female had a FTMH with focal VMT and visual acuity of 20/70 in her right eye. She underwent an injection of ocriplasmin and the VMT was released, but the FTMH persisted. Visual acuity declined to 20/400 3 days post injection. This patient underwent vitrectomy surgery with successful closure of the FTMH and achieved 20/40 postoperative visual acuity. However, she still had significant metamorphopsia and distortion and was not happy with her postoperative results. Six months later, she developed distortion due to VMT in her fellow eye and was faced with the possibility of another FTMH and surgery. At the time, her visual acuity was 20/25. She was well-educated regarding ocriplasmin in the setting of focal VMT and decided to proceed with another injection. One week following the injection, she had successful release of the focal VMT and resolution of the metamorphopsia and a return to 20/20 vision. She maintains 20/20 vision 9 months out, and is pleased with her treatment decision.

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Questions and Answers with the Experts

Do you have any tips for injecting ocriplasmin (Jetrea, Thrombogenics, Inc.)?

Allen C. Ho, MD: When administering the injection, I inject deeply. Unlike my usual needle passes, with ocriplasmin I am injecting all the way to the hub, attempting to get the drug through as much vitreous as I can and closest to the area of vitreomacular traction (VMT). I also lay the patient back for 30 to 60 minutes to allow gravity to promote distribution to the back of the eye.

What is your standard routine for follow-up after an injection of ocriplasmin?

Dr. Ho: My routine has evolved from a very close to a slightly more relaxed follow-up. I now let the patient rest 1 hour following the injection before imaging them. I then bring the patient back in 1 week for the first visit and go from there.

Mitchell S. Fineman, MD: I have also evolved in a similar manner. My first visit is 1 week post-injection, and then usually between 2 to 4 weeks after that.

One week post an injection, you are not seeing the anatomic outcome that you expected. Perhaps a patient has had release of VMT but not full-thickness macular hole (FTMH) closure, or he or she has not responded at all. What is your timing and routine for these patients?

Sunir J. Garg, MD: This is difficult. Ideally, the success at 1 week, which is the case most of the time. However, I have had a few patients who have release of VMT at week 1 but not resolution of FTMH yet. I have urged many of them to wait until a month has passed, as a reasonable percentage of those patients will see closure of FTMH within 1 month.

Carl D. Regillo, MD: I personally like to think about doing vitrectomy for a FTMH that has persisted about 1 month after an injection. However, I do not think the window is critical, and waiting even 2 months does not create greater harm.

Have you seen either VMT release or FTMH closure more than 28 days post injection?

Dr. Fineman: In my initial series of patients, there was 1 patient who did not have release of VMT following the injection and was offered vitrectomy surgery but declined. Several months later, he did have release of VMT. However, I believe that was a spontaneous release and not due to the ocriplasmin. The enzyme degrades fairly quickly, and I doubt the response to the drug was that delayed.

Do you have any concern with regards to post injection retinal tear or detachment?

Dr. Ho: Considering the activity of the drug and where it is intended to work, it is logical to consider retinal tears a possible risk. However, the clinical trial of approximately 700 patients, the post-marketing clinical experience, and our own experience here at Wills Eye really shows that the event rate of retinal tear and retinal detachment is quite low. I would consider it similar with other intravitreal injections not related to any pharmacologic effect of the vitreous.

While most of the adverse events are transient and subside after 1 week, are there cases of persistent decreased vision?

Dr. Garg: I think there is still a lot of work to do on this. I am hoping that the ORBIS study, a large, prospective phase 4 study, will help to answer some of these questions. While I do bring up these possible risks with my patients, I have not changed my practice patterns at this point. Good patient education, particularly about the dyschromatopsia early on, makes it a lot less stressful for the patient and the doctor as they experience it. I encourage my patients to take a long-term approach to treatment.

Dr. Regillo: It has to be stated that vision recovery is sometimes quite slow. We know that the subretinal fluid in the macula of a successful patient can persist for 2 to 4 months, and in a few cases, beyond that. The patient and the doctor need to be patient and have appropriate expectations.

I feel better now that we have had the drug for well over 1 year in practice and have follow-up well beyond the clinical studies. It has only improved my comfort with the safety level of the injection.

How do you put the intravitreal injection of ocriplasmin in perspective with other treatment options?

Dr. Ho: This drug is really a unique tool in our toolbox. There is no other pharmacologic option for VMT and FTMH, and if it does not work, you still have the surgical option. When we look at the efficacy and safety, we should be comparing it to surgery, the only other option. The risk of transient vision loss is around 7% but the rate of persistent vision loss would be less that 1%. That probably compares to surgery.

Similarly, ocriplasmin is not like an anti-VEGF injection that provides immediate positive results in nearly every patient. We have to prepare patients that they might get worse before they get better, and we should hone in on the best candidates, per Dr. Garg’s article.
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CME QUESTIONS

1 AMA PRA Category 1 Credit™

1. Current literature demonstrates that Stage 2 full-thickness macular holes (FTMH):
   a. Progress to larger holes and declining visual acuity rarely
   b. Progress to larger holes frequently, but do not impact vision
   c. Progress to larger holes more than 75% of the time, with declining visual acuity
   d. Progress to larger holes more than 75% of the time, but also spontaneously close about 20% of the time

2. Which of the following appears to have a positive association with release of VMT following ocriplasmin:
   a. Patients younger than 65
   b. Area of adhesion less than 1500 µm
   c. Presence of macular hole
   d. Phakic lens
   e. All of the above

3. What are the 3 most common side effects of ocriplasmin?
   a. Eye pain, blurriness, vision loss
   b. Vision loss, floaters, macular edema
   c. Ellipsoid changes, eye pain, floaters
   d. Vitreous floaters, eye pain, photopsia

4. Which of the following statements about macular hole closure rates in the MIVI-TRUST studies is not true?
   a. Macular holes larger than 400 µm have a closure rate of 7.7% when treated with ocriplasmin
   b. Macular holes from 250 to 400 µm have a closure rate of about 37% with ocriplasmin
   c. Macular holes less than or equal to 250 µm in size have a closure rate of almost 60% with ocriplasmin
   d. 70% of successful macular hole closures happen within the first 7 days following intravitreal injection

5. Following injection of ocriplasmin, follow up should include:
   a. Patient visits at days 1, 7, 14, and 21, with surgery scheduled immediately if the outcomes are not successful
   b. Patient visits at day 7 and 28, with surgery potentially scheduled within the following two months if outcomes are not successful
   c. Patient visits every two weeks for the first 6 months to monitor progress

6. True or False: While release of VMT or closure of FTMH is most likely within the first week, it could take up to 6 months for ocriplasmin to take effect?
   a. True
   b. False
**ACTIVITY EVALUATION**

<table>
<thead>
<tr>
<th><strong>Did the program meet the following educational objectives?</strong></th>
<th><strong>Agree</strong></th>
<th><strong>Neutral</strong></th>
<th><strong>Disagree</strong></th>
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<td>Explain the pathogenesis of VMA and its role in various retinal pathologies</td>
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<td>Identify the benefits of induced PVD vs anomalous PVD</td>
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<td>Discuss the available data on both surgical and pharmacologic PVD induction</td>
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<td>Differentiate between the various vitreolysis agents for PVD induction and their safety and efficacy profiles</td>
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Comments regarding commercial bias:
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If yes, please specify. We will contact you by email in 1 to 2 months to see if you have made this change.
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