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RETINA TODAY

CME ACTIVITY

Current Management of Vitreomacular Interface Disorders

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STATEMENT OF NEED

Symptomatic 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 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 VMT syndrome; and 56% in idiopathic epimacular membrane. The incidence of VMA in macular edema appears to depend on the severity of the underlying condition. In AMD, the rates vary but have been reported to be as high as 59% in exudative AMD.

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 PPV and more recently with small-gauge PPV 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.

There are data showing that nonsurgical induction of PVD using ocriplasmin, 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. 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 was shown to be safe and effective for PVD induction, providing further evidence that pharmacologic vitreolysis with ocriplasmin may provide a 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 vitreolysis agents and their differences, and the ability to identify patients who may benefit from PVD induction.


CONTENT SOURCE

This continuing medical (CME) activity captures content from a dinner meeting series, which took place during the Spring of 2013.

TARGET AUDIENCE

This certified CME activity will be 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
• Explain the mechanism of action of pharmacologic vitreolysis
• Discuss the available data on the safety and efficacy of vitreolysis agents for PVD induction
• Understand the importance of patient selection for pharmacologic PVD

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.

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FACULTY/STAFF DISCLOSURE DECLARATIONS
Dr. Regillo states that he receives grant research support from Alimera, Allergan, Genentech, Glaxo Smith Kline, Ophthotech, Regeneron, ThromboGenics, Advanced Cell Technology, Johnson and Johnson, QLT, and Alcon Laboratories, Inc. He is a consultant and speaker for Alimera, Alcon, Genentech, GlaxoSmithKline, and Regeneron.

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Current Management of Vitreomacular Interface Disorders

CURRENT MANAGEMENT OF VITREOMACULAR INTERFACE DISORDERS

By Carl D. Regillo, MD

Vitreomacular adhesion (VMA) is defined as any condition in which the vitreous is partially separated, but still attached, by varying degrees to the center of the macula. Within the spectrum of VMA is vitreomacular traction (VMT) with or without macular hole.

Historically, the treatment options that have been available for the vitreomacular interface (VMI) disorder of VMA have been either watch-and-wait or surgery. The watch-and-wait strategy has been used for mildly symptomatic VMT or macular holes, where visual acuity was relatively good. Larger holes and significantly symptomatic, progressive VMT have been addressed with vitrectomy, with the consideration of the benefit:risk ratio for the patient.

Natural History of VMT and Full-Thickness Macular Holes

The evidence for observation of VMT with and without macular hole is limited. Odrobina et al evaluated the natural history of VMT in a small case series of 19 patients with idiopathic VMT. Nine of these patients experienced vitreomacular release and 2 of these patients over the average period of observation of 8 months had normal optical coherence tomography (OCT) scans at the final visit. Even with spontaneous resolution or continued traction, the vast majority, 17 patients, had some sort of defect that could be detected clinically with decreased vision or anatomically by OCT on the final visit, including cystoid changes, lamellar macular holes, macular holes, inner/outer segment defects, or epiretinal membrane (ERM) formation. Very few patients normalized, even though approximately 40% had spontaneous release of the VMT.

Hikichi et al is a larger, retrospective study of 53 patients with symptomatic VMT with good long-term follow-up (~60 months). This study can provide some information on the natural course of VMT, but it is important to note that this is an older study that was pre-OCT, so there are limitations in the types of conclusions that are able to be drawn from these data. The spectrum of the cases that were included in this study is shown in Figure 1 (page 8). The study authors divided the cases of VMT into those with cystoid changes and those without. The majority had cystoid changes at baseline and those without. The majority had cystoid changes at baseline.

Most of the patients who had milder VMT (80%) developed cystoid changes and worsened to some degree, and 20% had no changes. Of the cases that were worse at baseline, most (79%) remained stable (but remember they had cystoid changes at baseline and significant disease) and only a small percentage, 5%, had spontaneous resolution of the VMT. Sixteen percent had some resolution of VMT with degenerative sequelae.

In the study, most patients had moderate to severe decreased visual acuity at baseline. Approximately 50% had moderate decreased vision between 20/50 and 20/100, and approximately 15% had vision of 20/200 or worse. Thirty-six percent of patients had visual acuity of 20/200 or worse, 36% had visual acuity between 20/50 and 20/100, and only 7% had visual acuity of 20/40 shifted toward more severe vision loss over time.

The natural history for the patients in this study was not good, but as previously noted, the disease that was included was mostly moderate to severe, for which most of us would operate rather than observe. The patients either stayed the same or became worse, few spontaneously resolved, and even fewer had true resolution of VMT.

The data from these 2 studies regarding the natural course of VMT demonstrate a spontaneous resolution rate in the range of 11% to 47%, which makes it difficult to know with certainty which VMT will spontaneously resolve and which will not. Time to resolution averaged from 8 to 15 months. An important finding from Hikichi et al is that when VMT progresses to moderate or severe stage, the natural history worsens.

Full-thickness macular (FTMH) holes are a more straightforward situation. Data show that FTMHs rarely close spontaneously, so often these will be managed surgically. We also know that approximately 75% of patients with small, early onset stage 2 holes will progress to larger, stage 3 or 4 holes, which tend to coincide with decreased visual acuity.

Surgery for VMA and FTMH

Several studies have shown that surgically induced anatomic resolution of VMT and FTMH leads to visual acuity gain. Witkin et al found a postoperative improvement in patients with VMT of 10 letters or more. Larsson and Rouhette et al found an improvement after surgery to resolve VMT of 15 letters or more. Ezra et al achieved a 15 letter or more gain in patients who had macular hole surgery, and Mester et al achieved a 20-letter or better visual acuity gain.

So what can we do? We know that surgical intervention...
can result in good visual acuity for significant VMT and even better results for macular holes. The success rate of surgery for complete closure of FTMH is high at 90%.

So when is it best to treat? For VMA, the large range in spontaneous resolution from the natural history studies is too vague to offer any solid guidance. We do know that visual acuity gets worse over time with observation and that the average time to resolution for eyes observed with VMA is long, opening up the window for significant visual loss. For FTMH, deciding when to treat is easier. The data show that FTMH close spontaneously in only 3% to 11% of cases and that most stage 2 holes will progress to stage 3 or 4.3

There are other data demonstrating that when compared to observation, surgery for stage 2 macular holes was associated with better visual acuity and smaller-diameter holes.

As with any surgical procedure, however, there are risks associated with better visual acuity and smaller-diameter holes.

A PHARMACOLOGIC OPTION

Until recently, observation (watch and wait) or surgery were the only viable options to manage the vitreomacular interface (VMI) disorder of VMA. Pharmacologic vitreolysis with the newly US Food and Drug Administration (FDA)-approved proteolytic enzyme, ocriplasmin (Jetrea, Thrombogenics), is a new option.

What is ocriplasmin? Ocriplasmin is the active enzymatic domain of plasmin that is produced by recombinant DNA technology. As a nonspecific protease, it will target key proteins in the vitreous gel including fibronectin, laminin, and collagen. By targeting those macromolecules in the vitreous body and at the VMI, the drug is designed to promote vitreous liquefaction and separation. Its success varies from patient to patient, a point that I will discuss in more detail further along in this article.

CLINICAL STUDIES WITH OCRIPLASMIN

There have been other phase 2 studies evaluating ocriplasmin’s utility for VMT associated with other disease states, such as age-related macular degeneration, retinal vein occlusion, and diabetic macular edema, but the MIVI-TRUST program (MIVI-006 and MIVI-007), which led to FDA approval focused on VMT and FTMH.12

The label for ocriplasmin specifically refers to its indication for symptomatic VMA. At the very beginning of this article, I refer to VMA as being a spectrum of disorders of the VMI. Figure 2 (page 8) shows what this spectrum looks like on OCT.

The MIVI-TRUST phase 3 trials that were conducted in the United States and Europe randomized 652 participants to injection with 100 mL of ocriplasmin 125 µg, compared to an active injection vehicle control of 100 mL saline ocriplasmin or placebo. The placebo injection was equal in volume to the drug, which was important for evaluating drug effect vs effect of liquid on posterior vitreous detachment (PVD). Patients enrolled in the trials were required to have symptomatic VMA with or without macular hole.

The primary endpoint was full pharmacologic resolution of VMA at 28 days. Secondary endpoints included complete PVD at day 28, nonsurgical closure of macular hole, change in visual acuity, and responses on a visual function questionnaire.

The adhesions in the study could be broad-based VMAs with or without ERM. There was an assortment of VMA severity from mild to severe, and there were cases of VMA with macular holes.

Patients were followed on day 7, 14, 28, 3 months, and 6 months postinjection and that was the endpoint to the study. After day 28, it was up to the investigator, but patients could go to surgery to release the VMA and/or close the macular hole. From day 28 to month 6, the data was difficult to interpret because it is a mix of the natural course of the disease changing over time with or without vitrectomy intervention.

Participants enrolled in the studies were required to have time-domain OCT-confirmed VMA and be symptomatic; however, visual acuity did not have to be decreased very much and, in fact, eyes with ETDRS visual acuity as good as 20/25 were included.

Exclusion criteria in this study were eyes with high myopia, -8 D or worse, any history of prior vitrectomy, that made sense, of course, or prior laser photocoagulation to the macula. Macular holes greater than 400 µm were also excluded; however, there was a small number of eyes with larger holes that were enrolled as protocol violations.
By Peter K. Kaiser, MD

Approximately 98% to 99% of the vitreous is composed of water, and the remaining 1% is made up of macromolecules, including glycoproteins, proteoglycans, collagens, glycosaminoglycans, and other structural proteins that bind the vitreous material and serve as a glue that holds the vitreous to the internal limiting membrane (ILM) of the retina. At birth, the vitreous is firm and attached to the retina, most strongly at the vitreous base, equator, over retinal blood vessels, and at the optic disc and macula. As we age, however, the vitreous gel begins to liquefy and come away from the retina. The ideal posterior vitreous detachment (PVD), which is common in people who are older than 50 years, involves a synergistic liquefaction and separation process. In the setting of an incomplete PVD, however, fine strands that are more firmly attached can pull on the retina, causing complications such as retinal tears or vitreomacular adhesion.

The process of vitreous liquefaction starts early in life—early as 4 years of age. When a person is in the middle to late teenage years, approximately 20% of the vitreous volume is liquid. The liquefied lacunae increase in number and size as a person ages, to the point where, by 70 years of age, approximately 50% of the vitreous is liquid.

There is progressive age-related weakening of the adhesion between the posterior vitreous cortex (posterior hyaloid) and the ILM. After age 60, there is significant correlation between degree of liquefaction and PVD, because at that point, the vitreoretinal adhesion becomes sufficiently weakened to allow separation. In addition to the vitreous status, there are changes that are also occurring at the vitreomacular interface.

**CHANGES TO THE VMI**

There are 4 states to a PVD. Stage 1 PVD begins in perifoveal macula, extending next into the superior and temporal midperiphery. In stage 2, the detachment goes to the fovea, and then to the inferior midperiphery in stage 3, finally reaching the optic disc margin in stage 4, resulting in a complete detachment, often including the Weiss ring.

The ideal PVD involves a synergistic liquefaction and separation process. In the setting of an incomplete PVD, however, fine strands that are more firmly attached can pull on the retina.

Most pathalogy at the vitreomacular interface occurs at the locations where the vitreous is most strongly adherent and are responses to the changing architecture. Incomplete PVD is associated with retinal tear, vitreopapillary traction, macular pucker (epiretinal membrane formation), vitreomacular traction, and macular hole. The size of the adhesion is important, because as an adhesion broadens, the likelihood of epiretinal membrane formation increases, making the vitreomacular adhesion more difficult to treat.

**PRIMARY ENDPOINT RESULTS**

The primary outcome, as previously noted, was resolution of VMA at day 28. In both the independent studies and the pooled data, there was a statistically significant difference between the ocriplasmin and placebo groups. The overall success rate in VMA resolution was 26.5% in the ocriplasmin arm vs 10% in the placebo arm (Figure 3, page 9).

Ocriplasmin is an enzyme that rapidly degrades. When injected in the vitreous, it cannot be detected beyond 24 hours, so it exerts its enzymatic effects quickly, and, if it is effective, vitreous liquefaction and/or vitreous separation occurs quickly. This is why the primary endpoint was set at 28 days, because if by day 28 the drug has not worked, it was thought that it would be unlikely to have an effect thereafter.

This is exactly how this played out in the clinical trials. In most cases, if the PVD was going to release successfully with ocriplasmin, it occurred in 70% of eyes within the first week, and 80% percent within the first 2 weeks (Figure 4, page 9).

Figure 5 (page 9) shows an example from the clinical trials. Although patients did not come back at day 1 and 2 after injection, for the most part, based on the symptoms and participants’ experience, we thought it was reasonable to think that separation happened quickly in those who experienced resolution of VMA within the first 2 weeks. At baseline, there is obvious VMT with cystic changes and 20/50 vision. By day 7, VMA resolution has occurred. This is a common theme for the successful cases of resolution.

Some patients’ visual acuity decreased after vitreous release from the macula and although the data cannot show definitively why this occurred, it may be due to new subretinal fluid that was observed under the center of the macula in anatomically successful cases. The decrease in visual acuity and corresponding subretinal fluid evident within the first week slowly improves over the ensuing weeks or months.

At 1 month, the subretinal fluid is decreasing and, at month 3 and month 6, as the anatomy improves, the visual acuity improvement follows. Beyond 6 months, the visual
Acuity could continue to improve, and a study for which we should soon have data, OASIS, will reveal the more long-term (2-year) outcomes.

**Subgroup Analysis**

Looking specifically at the subgroup of patients who had macular hole, the success rate was better. Approximately 40% had successful hole closure (Figure 6, page 10), demonstrating that VMA resolution promotes hole closure.

Interestingly, hole closure occurred in some cases without VMA resolution and vice versa. The important point is that macular hole closure is necessary to improve visual acuity, and in the clinical trials, macular holes closed 40% of the time and this occurred by day 28. If it did not occur by day 28, like PVD, it was not going to happen.

The trials showed that macular hole size mattered. For holes that were smaller than 250 µm, the success rate of closure approached 60%. For macular holes with a diameter between 250 µm and 400 µm, the success rate was 36.8%. Nineteen eyes violated protocol entry criteria with macular holes at baseline larger than 400 µm, and none of these closed. Clearly, pharmacologic vitreolysis does not appear to be adequate for closing larger holes and these patients should not be considered candidates for the drug in practice. If the eyes with larger holes had not been enrolled in the clinical trials per protocol, the overall macular hole closure success rates would likely have been higher in the study (Figure 7, page 10).

Figure 8 shows a small macular hole from the clinical trials. The OCTs demonstrate a pocket of subretinal fluid as was seen in the case in Figure 5 (page 9). VMA resolved by day 7, and the subretinal fluid remained. Unlike the previous case, however, visual acuity improved with macular hole closure. By month 6, the fluid had completely resolved and visual acuity was at its best improvement at 20/32.

**Safety of Ocriplasmin**

Overall, ocriplasmin was found to be safe in the phase 3 clinical trials. There were some ocular adverse events early after injection, which included vitreous floaters, eye pain, photopsia, blurred vision, and reduced visual acuity. The ocular adverse events at day 7 postinjection are seen in Figure 9 (page 11). These effects for the most part were transient, however, and beyond that first week, the event rates were well balanced with none being statistically significantly different from the control group (Figure 10, page 11). In some cases, as with reduced vision, the numbers were slightly higher in the placebo arms.

Adverse events were analyzed in different ways to determine the reasons why there was a difference at 1 week. For instance, with vision loss of 2 or more lines at 1 week, almost 8% of patients in the ocriplasmin groups lost 2 or more lines compared to 1.6% of those in the placebo arms.

What were the reasons for this? We found that it came down to 3 categories: (1) actual success; the VMA resolved but there was some subretinal fluid under the macula, such as in the cases in Figures 5 and 8 and demonstrated again in Figure 11 (page 11); (2) progression of VMT (Figure 12, page 12); and (3) progression of FTMH (Figure 13, page 12); in both VMT and FTMH, the drug either did not work or potentially made these conditions worse. Reasons number 2 and 3 are rare, but it can occur and highlights the need to discuss the drug and its effects with patients prior to injection to manage expectations and for the patient to understand that surgery may be needed sooner rather than later if there is worsening of their condition after injection of the drug.

The rates of retinal tear were relatively low in the ocriplasmin group, and for patients who went on to have a vitrectomy, those in the placebo group had a higher rate of retinal tear than those in the ocriplasmin group.

The rates of retinal detachment in the ocriplasmin group were also low, and again, in the post-vitrectomy group, retinal detachment rates were higher in the placebo group.

There was theoretical concern for drug-induced lens instability, because this enzyme has the potential to affect the lens zonules, but the incidence was very low (1 patient in the phase 3 MIVI-007 trial who went on to vitrectomy had some degree of lens instability that was noticed intraoperatively, and 1 pediatric patient in the phase 2 MIVI-09 trial in whom lens subluxation occurred at the time of vitrectomy).

There has been some observation regarding the side effect of dyschromatopsia that may occur to some degree after successful VMA resolution. The patient generally described this as a yellowish change in vision, and to date, the cause is unknown. Sixteen events in 820 subjects (2%) were reported in the FDA submission. Fourteen of 16 cases occurred, on average, at 1 day and resolved, on average, by 3 months. All incidents were rated as mild and none were serious, and the majority of the cases were reported to originate in a phase 2 trial from a single center. In this study, patients were prospectively asked whether they detected a color change in their vision. Note that in the phase 3 clinical trials, patients were not specifically asked about color vision changes. Although its true incidence in the phase 3 study may be underestimated for this reason, it is something that we hope to have more accurate data on in the future from the OASIS study.

**Does Patient Selection Matter?**

Subsequent to the subgroup analysis data being released, additional subgroup analysis was performed to look at independent variables that could portend success with ocriplasmin. Five independent variables were identified as statistically significant: (1) FTMH (eyes with FTMH had better results); (2) age (patients younger than 65 years of age had better results); (3) phakic status (eyes that were phakic had better results); (4) ERM (patients
without ERM had better results); and (5) area of VMA adhesion (more focal, less-than-1500-µm FTMH had better results). The results are seen in Figure 14 (page 12).

Figure 15 (page 13) shows a similar analysis in which independent variables were stacked. The numbers are small, which is important to consider, but it does demonstrate what the chances of success might be for a particular patient.

**SUMMARY**

Our practice has now performed over 20 intravitreal injections of ocriplasmin. We have looked back at our success rate thus far, and, like a good baseball hitter, we are batting just over 300 at this point. With continued refinement of patient selection based on the various subgroup analyses, we hope to achieve success in over 40% of our patients down the line.

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Figure 3. Overall success rate of ocriplasmin vs placebo injection in the phase 3 clinical trials.

Figure 4. Most cases in which VMA resolved did so within the first 2 weeks after injection.

Figure 5. OCT scans of a patient from the phase 3 clinical trials demonstrate a typical positive response to ocriplasmin.
Figure 6. The subgroup analyses demonstrated that ocriplasmin had higher success rates for macular hole closure.

Figure 7. If the eyes with larger holes had not been enrolled in the clinical trials per protocol, the overall macular hole closure success rates would likely have been higher in the study.

Figure 8. A small macular hole from the clinical trials. The OCTs demonstrate a pocket of subretinal fluid. VMA resolved by day 7, and the subretinal fluid remained. Unlike the previous case, however, visual acuity improved with macular hole closure. By month 6, the fluid had completely resolved and visual acuity was at its best improvement at 20/32.
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Figure 9. Ocular adverse events at day 7 postinjection.

Figure 10. These ocular adverse events from Figure 9 were, for the most part, transient, and week 1 to month 6, the event rates were well balanced with none being statistically significantly different from the control group.

Figure 11. VMA resolution with subretinal fluid under the macula.
Figure 12. Progression of VMT.

Figure 13. Progression of FTMH.

Figure 14. Subgroup analysis identified 5 independent variables that are markers for success with ocriplasmin: (1) FTMH (eyes with FTMH had better results); (2) age (patients younger than 65 years of age had better results); (3) phakic status (eyes that were phakic had better results); (4) ERM (patients without ERM had better results); and (5) area of VMA adhesion (more focal, less-than-1500-µm FTMH had better results).
A 62-year-old woman presented to me with blurred vision in her right eye (OD) that had persisted for 1 month. Her husband is an optometrist and he had obtained an OCT in which he detected vitreomacular adhesion (Figure A). Her vision at presentation was 20/40 OD.

I chose to watch and wait because the vision was not that bad and I knew that she would be monitored closely with frequent OCTs by her husband.

Six months later, nothing had changed OD, and her left eye (OS) was normal. At 8 months, however, her visual acuity OD had decreased to 20/80 and she was now significantly symptomatic. In addition, her left eye (OS) was showing signs of VMA (Figure B).

I injected the patient with ocriplasmin OD. The same case report: carl d. regillo, md (Continued on page 14)
night, she called and reported that she had severe flash-ers and floaters, with dyschromatopsia and decreased vision. When I saw her the next day, her vision OD was counting fingers only and her OCT showed release of the VMA with a small amount of submacular fluid (Figure C).

Given that there was successful VMA release and no other retinal problems other than the small area of cen-tral subretinal fluid, I advised close observation.

At the 1 week postinjection follow-up visit, the patient reported that her vision OD was steadily improving and that the flashes and floaters were subsid-ing. I obtained an OCT that showed persistent subreti-nal fluid (Figure D).

One month postinjection, cystic changes were still visible on OCT, but the subretinal fluid was gone (Figure E). The patient’s visual acuity was now 20/50 and she was feeling much better about the treatment because her vision overall was better compared to pretreatment. By month 3, the patient was very happy with her visual acuity as it continued to improve and was 20/40 (Figure F). Incidentally, the VMA in her left eye had spontane-ously released and the visual acuity in that eye had improved to 20/25.

At 6 months (Figure G) her visual acuity was 20/30 OD and 20/20 OS. At 12 months, her visual acuity was 20/20 in both eyes (Figure H). She was very happy with her results and considered both eyes to be completely normal in visual function.
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Name ___________________________________________________________ ☐ MD participant ☐ non-MD participant
Phone (required) ___________________________________________ ☐ E-mail (required) _______________________________
City _______________________________________________________________ State _________________________

CME QUESTIONS

1. By 70 years of age, what percentage of the vitreous is liquefied on average?
   a. 20%
   b. 30%
   c. 50%
   d. 80%

2. In the watch-and-wait approach for VMT (Hikichi study), what percentage of eyes with cystoid changes at baseline demonstrated spontaneous resolution?
   a. 5%
   b. 25%
   c. 50%

3. In the watch-and-wait approach for FTMH (Hikichi study), what percentage of stage 2 FTMH progress to stage 3/4?
   a. ~3%
   b. ~10%
   c. ~50%
   d. ~75%

4. In the phase 3 MIVI-TRUST clinical trial, positive independent baseline features identified for VMA resolution at day 28 include all of the following except:
   a. age <65 years
   b. FTMH absent
   c. VMA diameter ≤1500 µm
   d. ERM absent
   e. phakic

5. In the MIVI-TRUST clinical trial program (MIVI-006/007), pharmacologic closure of FTMH at month 6 demonstrated:
   a. significantly better closure with ocriplasmin in eyes with FTMH width <400 µm at baseline
   b. significantly better closure with ocriplasmin in eyes with FTMH width >400 µm at baseline
   c. no difference with placebo or ocriplasmin in eyes with FTMH width >400 µm at baseline
   d. a and c

6. In the MIVI-TRUST clinical trial program (MIVI-006/007), ocular adverse events in eyes with placebo were generally:
   a. lower than in eyes with ocriplasmin during days 0 to 7 and during day 8 to month 6
   b. higher than in eyes with ocriplasmin during days 0 to 7, but similar during day 8 to month 6
   c. the same as in eyes with ocriplasmin during days 0 to 7 and during day 8 to month 6
   d. lower than in eyes with ocriplasmin during days 0 to 7, but higher during day 8 to month 6

Did the program meet the following educational objectives?

| Explain the process by which VMA occurs | Agree | Neutral | Disagree |
| Identify the clinical implications of anomalous PVD | | | |
| Explain the mechanism of action of pharmacologic vitreolysis | | | |
| Discuss the available data on the safety and efficacy of vitreolysis agents for PVD induction | | | |
| Understand the importance of patient selection for pharmacologic vitreolysis | | | |

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Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME). Please complete the following course evaluation and return it via fax to FAX # 610-771-4443.

Name and email ____________________________________________________________________________________

Do you feel the program was educationally sound and commercially balanced? □ Yes □ No

Comments regarding commercial bias:
______________________________________________________________________________________________
______________________________________________________________________________________________
______________________________________________________________________________________________

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low ______

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low ______

Would you recommend this program to a colleague? □ Yes □ No

Do you feel the information presented will change your patient care? □ Yes □ No

If yes, please specify. We will contact you by email in 1 to 2 months to see if you have made this change.
______________________________________________________________________________________________
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If no, please identify the barriers to change.
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Please list any additional topics you would like to have covered in future Dulaney Foundation CME activities or other suggestions or comments.
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