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RETHINK VITREOMACULAR TRACTION

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The Underlying Anatomy of Vitreous and Its Role in Retinal Disease

BY J. SEBAG, MD, FACS, FRCOPHTH, FARVO

Vitreous is a remarkable structure. It is 98% water, but owing to the 2% structural macromolecules, vitreous maintains an exquisite gel structure. Those structural macromolecules are hyaluronan, which is a glycosaminoglycan of repeating disaccharide units, and collagen. Because hyaluronan is very hydrophilic and absorbs water, where it goes, water follows. Hylauronan is also organized within an entangled network that creates viscoelasticity, an important biophysical property. Collagen is the "skeleton" of the vitreous body. The most prevalent subtype of collagen that comprises the human vitreous is type II. The only other place in the human body that type II collagen is found abundantly is the articular cartridge in the joints. In both the joints and vitreous, there are many simultaneous manifestations of inborn congenital errors. An organization of collagen and hyaluronan exists within the vitreous, so that the collagen fibrils are spread apart by the hyaluronan molecules, maximizing the number of photons that penetrate the vitreous and access the retina, where vision begins.[1]

VITREOUS AGING

We have studied vitreous structure using dark-field slit-lamp microscopy. Figure 1 shows the appearance of the vitreous from a 33-week-old week old human embryo. There are no visible structures within the vitreous body, except for the remnant of Cloquet's canal, which is oriented toward the prepapillary posterior vitreous cortex. By middle age (Figure 2A), there are fibers within the vitreous body that have an anterior-posterior orientation arising from the vitreous base, and coursing posteriorly to insert into the posterior vitreous cortex. By old age (Figure 2B), these fibers have become aggregated and tortuous and are associated with pockets of liquefied vitreous.[2,3]

Transmission electron microscopy has demonstrated that these fibers consist of parallel collagen fibrils organized in bundles. It was previously thought that collagen fibrils inserted directly into the retina, but we now know that there is an extracellular matrix interface that mediates the vitreous adherence to the retina, which can be targeted by pharmacologic vitreolysis.

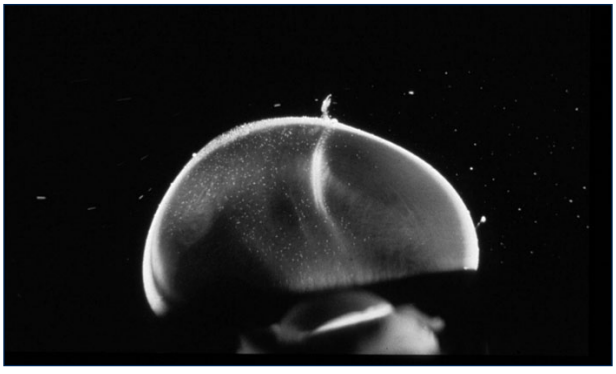

Figure 1. The appearance of the vitreous from a 33-week-old human embryo.

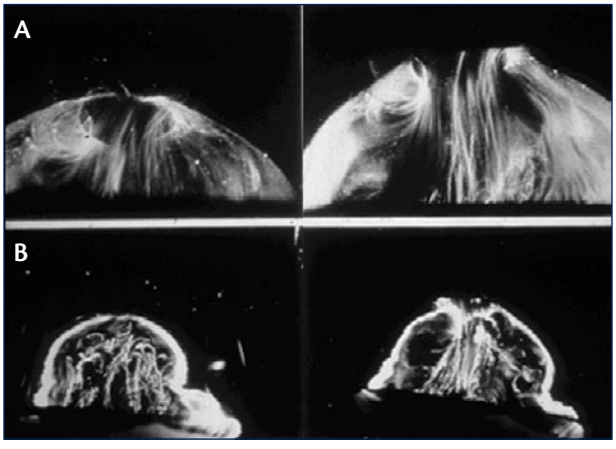

Figure 2. By middle age, there are fibers within the vitreous body that have an anterior-posterior orientation arising from the vitreous base, and coursing posteriorly to insert into the posterior vitreous cortex (A). By old age, these fibers have become aggregated and tortuous and are associated with pockets of liquefied vitreous (B).

The outer vitreous is organized in sheets, or lamellae. These lamellar sheets are important, as they represent potential cleavage planes that occur either during aging and posterior vitreous detachment (PVD), or during surgically induced PVD. Such a split is called vitreoschisis, an important manifestation of anomalous PVD.

Q&A WITH ANSELM KAMPIK, MD; J. SEBAG, MD; AND RAMIN TADAYONI, MD

Anselm Kampik, MD: Does the vitreous have the same molecular structure as the cornea?

J. Sebag, MD: Yes. In fact, the molecular constituents of the cornea and vitreous are the same. The difference is in hydration: To work well, the cornea requires dehydration but vitreous requires hydration.

Dr. Kampik: Is the collagen type of the zonules the same as in the vitreous and the vitreomacular interface?

Dr. Sebag: No. The zonular fibers are made of elastin, which is a different protein than the collagen structure of the vitreous. This is why ocriplasmin injections do not result in lens dislocation.

Dr. Kampik: How do you quantify metamorphopsia?

Ramin Tayadoni, MD, PhD: There is no good way to quantify metamorphopsia—we can only rely on the patient's subjective reports. It is rare, however, that a patient will describe metamorphopsia with no decrease in vision.

Dr. Kampik: What is more important and would cause you to consider intervention with an injection of ocriplasmin or surgery: reduced visual acuity or metamorphopsia?

Dr. Tayadoni: If a patient has good visual acuity but metamorphopsia, I would be hesitant to do surgery. There is no guarantee a patient will have good vision after surgery. I present the risks and have patients think it over before making any decisions.

Dr. Sebag: It is important to evaluate a patient's symptoms. The worst scenario is if a patient with minor or no symptoms is treated and becomes symptomatic as a result. The secret is to identify patients with bothersome symptoms, try to understand the source, and help them based upon their expectations.

Dr. Kampik: This is an important point. We do not treat symptoms or optical coherence tomogarphy (OCT) findings, but patients. How do you measure the size of the macular hole on spectral domain (SD)-OCT? Is it the same as with time-domain OCT? Is it different? And what are the other criteria you are looking for on OCT?

Dr. Tayadoni: It is easier with SD-OCT, because it is easier to use calipers to measure from the scans that can be taken around the area of the hole and we are able to choose a scan where the hole is widest or most narrow.

THE MECHANISM OF POSTERIOR VITREOUS DETACHMENT

The underlying anatomy of the vitreous is important to keep in mind when considering disease of the vitreomacular interface (VMI) and how to approach treatment. Although we know that aging changes the VMI, it remains unclear as to exactly how vitreous adheres to retina. However, we do know that the vitreous is firmer during youth than later in life.[3] The source of the adhesion remains partially unclear, but is an important consideration in the design of agents to induce PVD.

PVD is the most common event in the life of the human vitreous, occurring in 2 out of 3 individuals over the age of 65. It is important to remember that for a PVD to be innocuous, 2 things must happen at the same time: liquefaction of the gel and weakening at the vitreoretinal interface. When these occur in tandem, the separation is clean and, other than some vitreous floaters, there are no untoward effects. Liquefaction without dehiscence, however, results in anomalous PVD. The manifestations of anomalous PVD vary, depending upon where the gel is most liquefied and where the vitreous is most firmly adhered to the retina.

In 2004, I proposed the notion of anomalous PVD as a unifying concept of various disparate diseases ranging from retinal tears and detachments to macular holes and pucker. These were previously considered to be very different disease states, but when considered from the perspective of anomalous PVD, one can begin to understand how these are various manifestations of the same underlying problem.

When liquefaction occurs with separation of the

peripheral vitreous but persistent adhesion of full thickness posterior vitreous cortex to the macula, axial traction in an anterior-posterior direction can result, which plays an important role in VMT syndrome, such as in this extreme case in Figure 3, where combined scanning laser ophthalmoscopy (SLO)/optical coherence tomography (OCT) imaging shows elevation of the central macula by vitreous that has separated peripherally, but that has remained adherent to the macular region.

ANOMALOUS POSTERIOR VITREOUS DETACHMENT AND RETINAL DISEASE

Anomalous PVD can also influence wet age-related macular degeneration (AMD). The previous belief was that 3 out of 4 elderly patients had already undergone PVD, since they were all elderly. However, Susanne Binder, MD, made the observation that in cases for which she performed submacular surgery to remove choroidal neovascularization (CNV), which was a more common practice in the past, a high proportion of patients' vitreous was still attached to the macula (83%).[4] To corroborate this, we performed a study using ultrasound to diagnose total PVD and OCT to diagnose vitreomacular adhesion (VMA).[5] We found a 2-fold higher prevalence of total PVD, as diagnosed by ultrasound, in patients who had dry AMD, as compared to controls in patients who had wet AMD. By OCT, there was a four-fold higher incidence of VMA in wet AMD as compared to dry AMD.

Another manifestation of anomalous PVD is vitreoschisis—splitting of the posterior vitreous cortex, in which the outer layer of vitreous remains adherent to the macula while the rest of the vitreous pulls away. The remnant layer can cause tangential traction on the macula. This may play an important role in macular pucker and macular hole. In fact, we performed a study where vitreoschisis was identified in approximately half of patients with macular pucker or full-thickness macular holes (FTMH).[6,7]

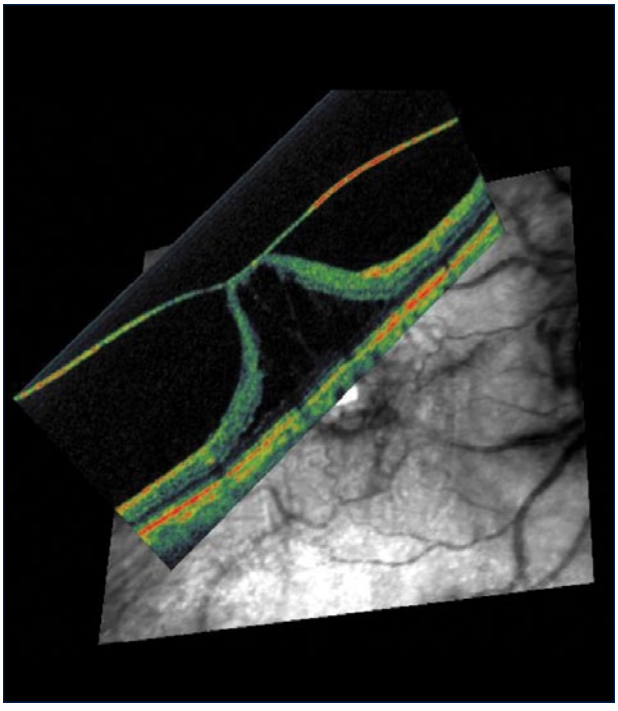

Figure 3. VMT syndrome. Combined scanning laser ophthalmoscopy (SLO)/optical coherence tomography (OCT) imaging shows elevation of the central macula by vitreous that has separated peripherally, but that has remained adherent to the macular region.

An important characteristic of FTMH is persistent vitreopapillary adhesion to the optic disc, found in 87.5% of cases.[8] This likely causes the tangential forces in a macular hole to be opposite that of macular pucker, where the incidence of vitreopapillary adhesion is 17.9%. The layer that is still attached in macular pucker contracts inward (centripetally), rippling the macula. In FTMH, the forces are outward, (centrifugally) opening a dehiscence in the central macula and creating a hole.

TABLE 1. INTERNATIONAL VITREOMACULAR STUDY (IVTS) GROUP CLASSIFICATION 2013

Classification	Sub-Classification
Vitreomacular Adhesion (VMA)	focal (≤1500 µm) or broad (>1500 µm) isolated or concurrent with other diseases no structural abnormalities in retina
Vitreomacular Traction (VMT)	focal (≤1500 µm) or broad (>1500 µm) isolated or concurrent with other diseases structural abnormalities in macula
Full-thickness Macular Hole (FTMH)	small (≤250 µm), medium (>250 µm and ≤400 µm), or large (>400 µm) with or without VMT primary or secondary to other conditions

NEW CLASSIFICATION SYSTEM FOR VITREOMACULAR INTERFACE DISORDERS

The increased knowledge that has emerged regarding the vitreous allowed for the 2013 introduction by an international panel of a new classification system.[9] The principles behind the classification system include the following: (1) that it be strictly anatomic (ie, based upon OCT); (2) that it be based on symptoms and not based on clinical findings; (3) that it be simple and easy to use; and (4) that it be predictive of outcomes both with surgery or pharmacologic vitreolysis.

The classifications and subclassifications are seen in Table 1. The classifications are divided into 3 categories: VMA, VMT, and FTMH. VMA is subclassified as focal (≤1500 µm) or broad (>1500 µm), isolated or concurrent with other diseases, and without structural abnormalities. VMT is subclassified as either (≤1500 µm) or broad (>1500 µm), isolated or concurrent with other diseases, and with structural abnormalities in the macula. FTMH is subclassified into small (≤250 µm), medium (>250 µm and ≤400 µm), large (>400 µm), with or without VMT, and primary or secondary to other conditions.

It is with this classification system that we hope to identify patients who will benefit from interventional procedures to manage disorders of the vitreous. ■

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Pathology of the Vitreomacular Interface

BY ANSELM KAMPIK, MD

Posterior vitreous detachment (PVD) is a common event in the course of human life, but spontaneous complete vitreous detachment has been shown to be infrequent.[1]

Vitreoschisis, a unifying concept describing incomplete PVD in which collagen and cells are left firmly attached to the internal limiting membrane (ILM), is common in many eyes, particularly in patients with diseases at the vitreomacular interface (VMI). Depending on the level of schisis, different pathologies may occur and include: the development of epiretinal membrane (ERM), which is a fibrocellular proliferation on top of the inner retinal surface; vitreomacular traction (VMT), which is persistent focal or multifocal attachment of vitreous to the macula, with tractional forces at the retina (with or without ERM); and macular hole, which is a full-thickness interruption of the fovea from tractional vitreal forces that is sometimes associated with ERM.

EPIRETINAL MEMBRANE

Cell types that have been identified in surgical specimens of ERMs include hyalocytes, glial cells (Müller cells, fibrous astrocytes, microglia), retinal pigment epithelium (RPE) cells, fibrocytes, myofibroblasts, and blood-borne immune cells such as macrophages. In 1981, we performed a comparative study of 56 cases of ERM and vitreous membranes in which we described those cells and the different collagen components of ERMs derived from electronmicroscopy of surgical specimens.[2] Gandorfer et al also noted a multilayered appearance of ERM and cellular proliferations demonstrating in many cases a layer of native vitreous collagen in between the inner limiting lamina (ILM) of the retina and the proliferating cells in a small study that was performed to assess the ultrastructure of the VMI in patients with VMT. Thus, there might be collagen and proliferating cells left behind on top of the ILM even after surgical peeling of an ERM.[3]

The ILM and/or vitreous collagen serves as a scaffold for cellular proliferation; adhesion of vitreous collagen transmits tangential tractional forces to the retina.

VITREOMACULAR TRACTION

There is a remarkable variation in the morphology of VMT. Similar to ERM, fibrocellular tissue develops over the macula. VMT can be either antero-posterior or tangential. The extent of the area of traction in VMT is usually more distinct as compared to the broader area of ERMs.

There is a remarkable variation in the morphology of VMT ... The extent of the area of traction in VMT is usually more distinct as compared to the broader area of ERMs.

There are 2 patterns of VMT. In type 1, collagen lies between the ILM and proliferating cells. In type 2, single cells sit on the ILM and there is little collagen present. The types of cells involved may be different in numeric composition compared with ERM, and there are some data that show a high proportion of myofibroblasts, but the number of specimens is too few to make any conclusions.[3]

MACULAR HOLE

In macular holes, vitreous collagen and some vitreous cells (hyalocytes) adhere firmly to the ILM. Sometimes cells are directly on top of the ILM.[4] An incomplete PVD can result in a macular hole, and as the vitreous cells remain at the ILM within the vitreous cortex, they might have the potential to drive cellular proliferation on the ILM. The retinal glial cells (Müller cells and astrocytes) may migrate from the retinal side of the ILM to the vitreal side to form additional ERMs in macular holes, which is possibly a late-stage phenomenon.

There are growth factors at the VMI that contribute to the adhesion of vitreous collagen to the ILM and may also contribute to fibrocellular proliferation at the retinal surface in the presence of vitreous remnants that include laminin and fibronectin.

Gandorfer et al showed fibrocellular proliferation within flat-mounted surgical ILM specimens from the macular hole rim.[5] Importantly, this study showed that there is

Epiretinal membrane, VMT, and macular hole are similar with regard to cellular composition, extracellular matrix modulation, and deformation of the macula, with differing clinical phenotypes.

often native vitreous collagen on top of the ILM reaching to the rim of the macular hole possibly exerting the traction from epiretinal clusters of cells that are distant from the edge of the hole.

SUMMARY

Epiretinal membrane, VMT, and macular hole are similar with regard to cellular composition, extracellular matrix modulation, and deformation of the macula, with differing clinical phenotypes. These findings support the unifying concept of vitreoschisis and that anomalous PVD may be a major factor in these pathologies. Our increased understanding of the process of PVD and advances in retinal imaging have led to the knowledge that there are 2 types of VMI disease: one in which collagen with cells on the vitreal side is adhered to the ILM, which, as we will learn within this supplement, responds to enzymatic vitreolysis; and one in which dense fibrocellular proliferation directly on the ILM without native vitreous collagen interspersed, responding better to surgery. ■

Anselm Kampik, MD, is Professor and Chairman of the Department of Ophthalmology at Ludwig Maximilians University Munich in Germany.

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Early Research on Ocriplasmin for Pharmacovitreolysis

BY ANSELM KAMPIK, MD

For many years, the effects of vitreomacular traction on various pathologies have been examined. With the knowledge that complete posterior vitreous detachment (PVD) is a rare occurrence, many of us in the retina subspecialty began to look at the possibilities for dissolving vitreomacular adhesion enzymatically.

EARLY STUDIES WITH PLASMIN

Based upon the initial research performed by J. Sebag, MD, Arnd Gandorfer, MD, and colleagues (including myself) performed some studies in animal eyes to see what, among the agents described so far by different authors, would be most effective for inducing a PVD in a porcine eye.[1] At the time, our group found that the only reliable agent for induction of a PVD in a porcine eye was plasmin.

Plasmin is a nonspecific serine proteinase that affects laminin and fibronectin, facilitating PVD. However, it also activates metalloproteinases, which may explain why plasmin can take a longer time to work than its actual activity.

The advantage of plasmin compared to other drugs developed for pharmaceutical vitreolysis is that it does not degrade collagen—a major component of the eye—but rather acts on type IV collagen and the native vitreous collagen while not affecting the newly formed vitreous collagen in some pathologic conditions. The disadvantage to plasmin is that it is not readily available for clinical use and that it is autologous and unstable by nature.

Dr. Gandorfer performed studies on human eyes with plasmin that were similar to those performed on porcine eyes and found that PVD occurred much the same way.[2] At the time, it was still unknown how much plasmin was required to induce PVD.

Gandorfer et al used 1 unit of plasmin for 30 and 60 minutes and 2 units for 30 and 60 minutes. Table 1 shows the results.

The reaction was dose dependent with 2 units being necessary for induction of a PVD posterior to the vitreous base. We were surprised to find that plasmin did not attack the vitreous base, which lowers the risk of retinal detachment. We also found, however, that 2 units of plasmin cannot be extracted from a patient's autologous in a reliable manner.

OCRIPLASMIN

At the time, ocriplasmin, known then as microplasmin, was being investigated for ischemic stroke. Knowing that this is a recombinant truncated form of human plasmin, we repeated all the earlier studies with ocriplasmin. We found

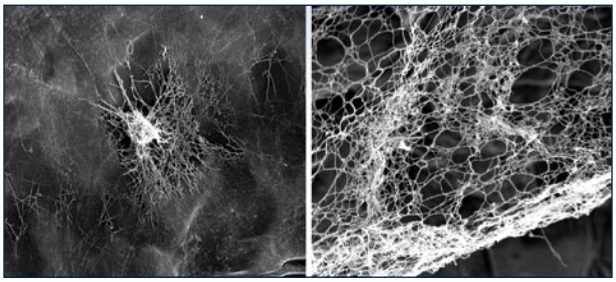

Figure 1. An eye injected with 14.25 µg of ocriplasmin at 3 days compared with a control eye with the area of adhesion.*

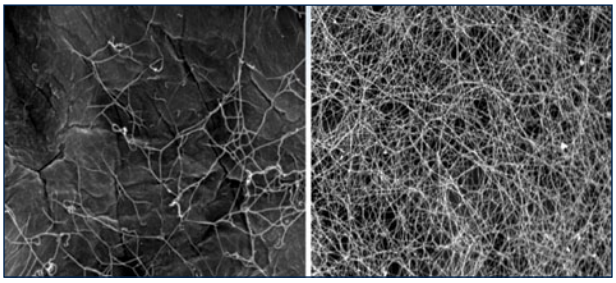

Figure 2. After injection of 25 µg of ocriplasmin, remnants of the adhesion can be seen at day 1, but there are far fewer collagen fibers present on the retinal surface compared with the control eye.*

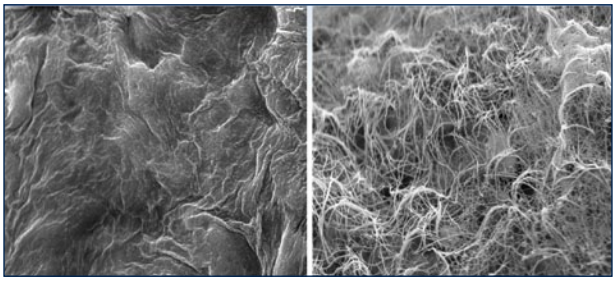

Figure 3. The same eye as in Figure 2. By day 3, complete separation is achieved.

*Each vial of JETREA® contains 0.5 mg of ocriplasmin in 0.2 mL solution. The recommended treatment dose is 0.125 mg (0.1 mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose. Full Prescribing Information for JETREA® can be found on page 20.

TABLE 1. THE RESULTS OF A STUDY SHOWING THE RESPONSE OF HUMAN EYES TO 1 AND 2 UNITS OF PLASMIN FOR 30 AND 60 MINUTES TO INDUCE PVD (+ = PVD; - = NO PVD)

Treatment	Number of Eyes	Remnants of Vitreous Cortex		
		Posterior Pole	Equator	Vitreous Base
1 U Plasmin 30 minutes	5	++ ++ ++ ++ ++	++ ++ +++ ++ ++	+++ +++ +++ +++ +++
1 U Plasmin 60 minutes	5	+ + + + ++	+ ++ + + ++	+++ +++ +++ +++ +++
2 U Plasmin 30 minutes	5	+ + + – +	+ + + + +	+++ +++ +++ +++ +++
2 U Plasmin 60 minutes	5	- - - - -	+ + + + +	+++ +++ +++ +++ +++

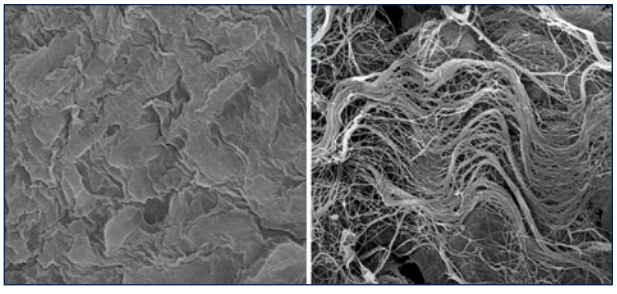

Figure 4. The same eye as in Figures 2 and 3. At 3 weeks the separation is even cleaner and there are no collagen remnants on the retinal surface.

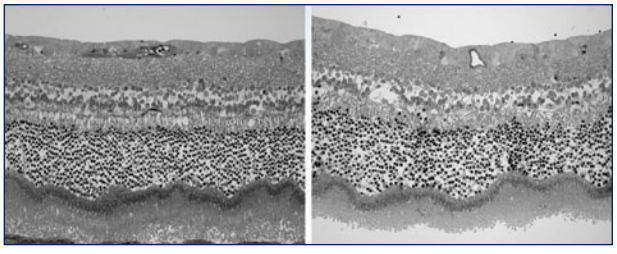

Figure 5. The immunohistology of the eye in Figures 2 to 4 did not differ from the control eye, demonstrating that this agent acts only on the vitreoretinal interface and the vitreous.

that vitreous separation with ocriplasmin is both dose and time dependent, that complete vitreoretinal separation is possible, that there is no alteration of retinal morphology, and that there is no alteration of the antigen reaction of neurons and glial cells.[3]

Two doses of ocriplasmin, 14.25 µg and 25 µg, were injected into feline eyes. We evaluated the eye on scanning and transmission electron microscopy at 1 day, 3 days, and 3 weeks.

Figure 1 shows an eye injected with 14.25 µg of ocriplasmin at 3 days compared with a control eye with the area of adhesion. After injection of 25 µg of ocriplasmin, remnants of the adhesion can be seen at day 1 (Figure 2), but there are far fewer collagen fibers present on the retinal surface compared with the control eye. In that same eye, by day 3 (Figure 3), complete separation is achieved. At 3 weeks (Figure 4) the separation is even cleaner and there are no collagen remnants on the retinal surface. The immunohistology, as seen in Figure 5 did not differ from the control eye, demonstrating that this agent acts only on the vitreoretinal interface and the vitreous.

SUMMARY

Based upon these collected data, we designed the phase 1 clinical trial to evaluate ocriplasmin to determine whether we could achieve a reliable, safe PVD with this enzyme without the need for surgery. The data from these clinical trials will be discussed by Pravin U. Dugel, MD, on page 13. ■

Anselm Kampik, MD, is Professor and Chairman of the Department of Ophthalmology at Ludwig Maximilians University Munich in Germany.

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Vitreomacular Interface Diseases: Symptoms and Diagnosis and Current Treatment Paradigms

BY RAMIN TADAYONI, MD, PHD

The diseases of the vitreomacular interface (VMI) include those in which the vitreous is attached to the macula and conditions in which the vitreous is detached from the macula. Vitreomacular traction (VMT) and full-thickness macular hole (FTMH) occur when the vitreous is attached, and epiretinal membranes (ERM), pseudo macular hole (MH) and lamellar macular hole (LMH) occur when the vitreous is detached. The complications of these include anomalous posterior vitreous detachment (PVD) and they all share common symptoms, which are identifiable thanks to advances in retinal imaging. Symptoms include visual acuity loss, central microscotoma, and metamorphopsia. These symptoms, however, can go undetected by patients if they occur in the nondominant eye.

DIAGNOSES FOR VMI DISEASES

The diagnostic assessment remains critical for management of VMI disorders and includes fundus imaging and optical coherence tomography (OCT), which can be used in concert for a cross-sagittal analysis. Figure 1 shows example of impending MHs on biomicrospic imaging with VMT and no ERM.

Figure 2 shows a case of VMT where an ERM is present. The 3D imaging shows a proliferation of the membrane, changing the prognosis of disease. The posterior hyaloid often adheres to the macula via the ERM as seen in Figure 3.

The availability of advanced imaging has made it easier to classify diseases of the VMI and determine when treatment is appropriate (Figure 4). The 2013 International Classification System for Vitreomacular Adhesion (VMA), VMT, and FTMH, as described by J. Sebag, MD, FACS, FRCOphth, FARVO, defines these conditions more clearly, describing the state of the vitreous (attached or detached and location of the attachment and/or the detachment) and the FTMH size, which is an important prognostic factor.[1] Figure 5 shows the rate of macular hole closure in respect to the baseline macular hole size in a series of 83 patients, in which macular hole <400 µm has a higher rate of macular hole closure compared to ≥400 µm.[2] Figure 6 shows fluorescein angiography (FA) and OCT images of a FTMH, LMH, and pseudo MH.

Epiretinal membrane is easy to diagnose on red-free and blue reflectance fundus imaging (Figure 7) and can be done via this modality even easier than on OCT. Optical

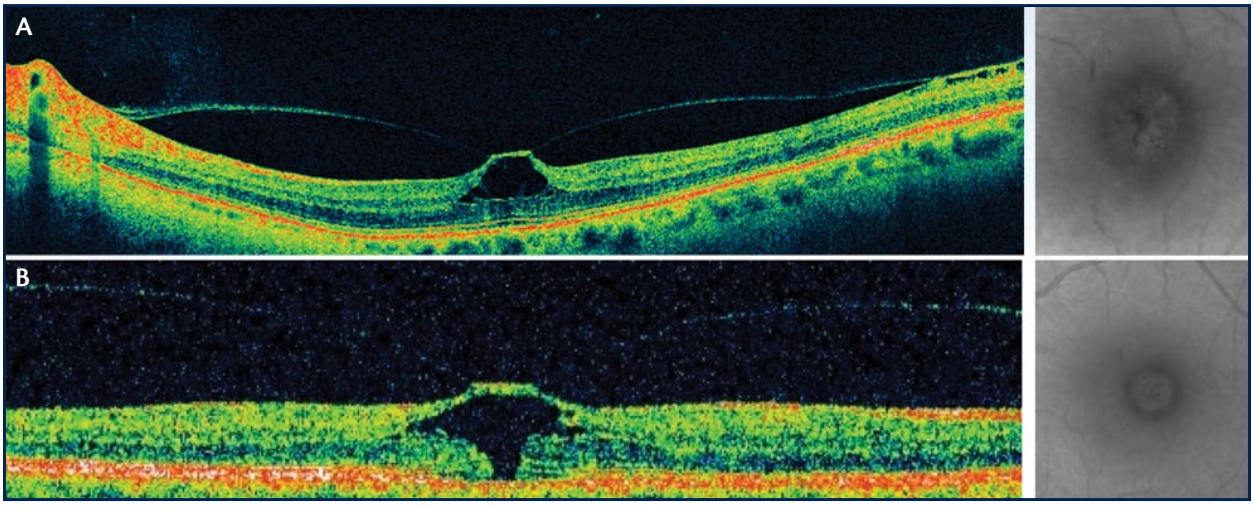

Figure 1. Impending MH: VMT and no ERM. Loss of foveal depression and a foveal yellow spot are seen. There is no vitreofoveal separation, but there is a change in macular pigment (A). Occult MH with a foveal yellow ring, radial striae, and a change in macular pigment (B).

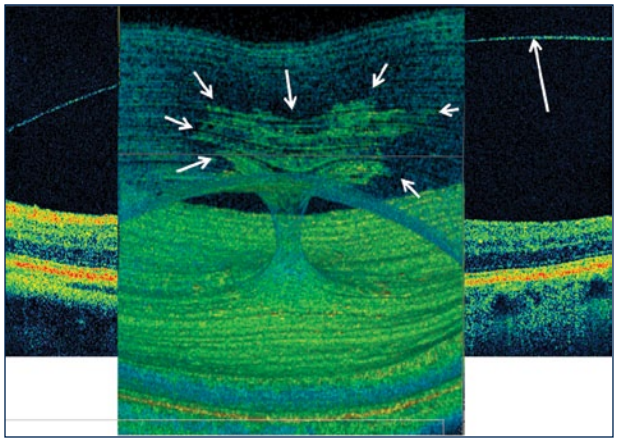

Figure 2. Three-dimensional OCT of VMT with ERM shows a proliferation of the membrane, changing the prognosis of the disease.

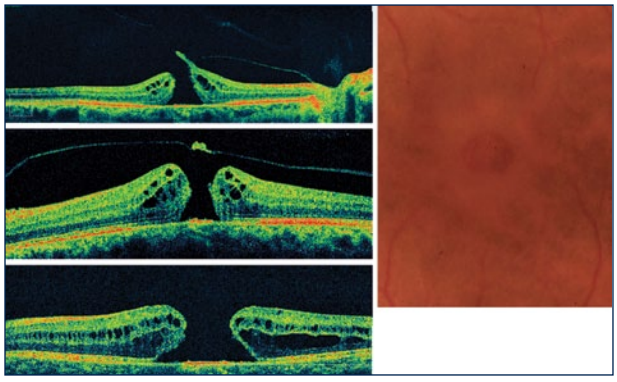

Figure 4. Optical coherence tomography makes classifying the status of the vitreous and the size of FTMHs easier.

coherence tomography is most important to determine the retinal thickness, which, along with ERM, is directly related to visual acuity. In some cases, retinal cysts are seen on OCT, which will most likely preclude surgery.

In FTMH, it is important to consider the risk of MH in the patient's fellow eye. Patients with MH in 1 eye are at varying degrees of risk for developing macular hole in the fellow eye, from between 5% to 16%. Patients with a complete PVD are at very low risk, but if VMA is present and there are changes in the center of the macula, then the risk is evaluated as high as 42%.[3] Patients with perifoveal PVD in the fellow eye should be followed closely.

TREATMENT OF VMI DISORDERS

Until recently, the only treatment for VMT (including when associated with MH ≤400 µm) was surgery, prior to which a careful analysis of the risk/benefit ratio is required weighing whether the improvement in vision vs the risks of a surgical procedure. The complications of posterior segment surgery include cataract formation, endophthalmitis, and retinal detachment. For most patients, surgery is not considered unless vision is 20/80 (0.6 LogMAR) or worse, except for a small number of

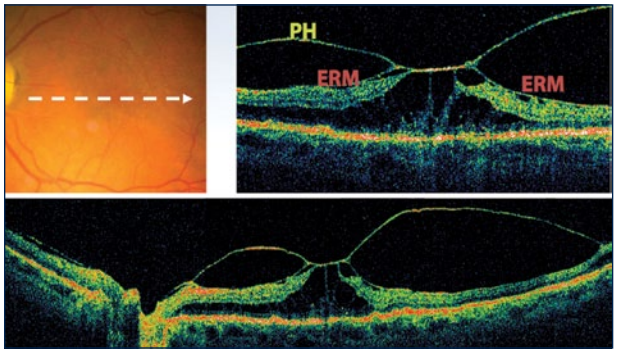

Figure 3. Adherent posterior hyaloid (marked PH).

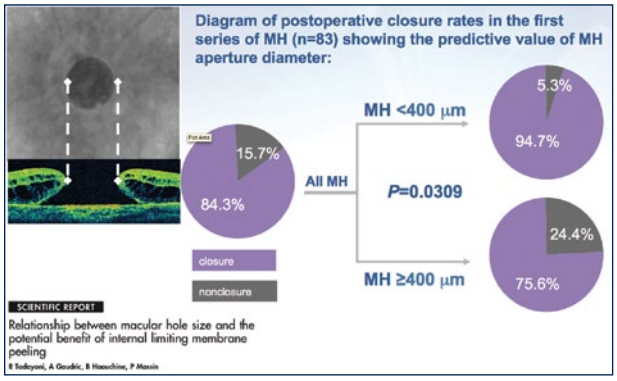

Figure 5. Diagram of postoperative closure rates in a series of MH (n=83) showing the predictive value of MH aperture diameter.

patients with metaphorphopsia. If there is a chance for spontaneous resolution, no intervention is warranted.

Vitreomacular traction with no ERM. Cases of impending MH, or VMT with no ERM, often will resolve spontaneously, so my general recommendation is to utilize a watch-and-wait strategy in these scenarios for at least 3 months. Again, if visual acuity falls below 20/80, or the VMA, MH, or VMT is long-standing and does not appear to be resolving, we will perform vitrectomy with the goal of detaching the adhesion.

Vitreomacular traction with ERM. Spontaneous release in cases of idiopathic VMT, or VMT with ERM is possible, but the incidences are rare. Most cases never release because the ERM acts as a cementing force between the vitreous and the retina. Surgery is usually recommended for cases where visual acuity is below 20/80; the ERM is peeled and the vitreous is removed along with it (Figure 8). Waiting too long to intervene can result in good anatomical, yet poor functional, results.

Full-thickness macular holes. For FTMH, size is important in the treatment decision process. In a study that my colleagues and I performed on FTMH closure, we found that all macular holes that spontaneously closed were smaller than 250 µm.[4] In most cases, closure occurs within the first 3 months of follow-up. If spontaneous closure does not occur, we consider intervention because we do not want the holes to become larger.

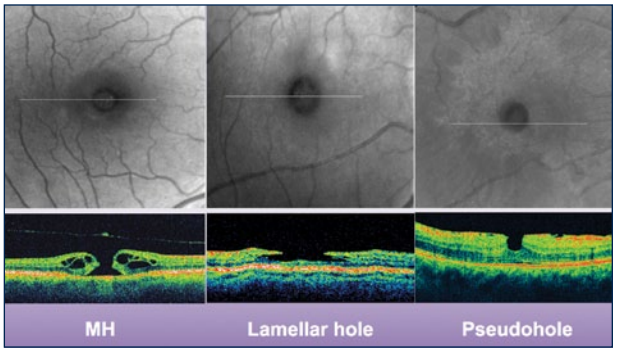

Figure 6. Fluorescein angiography and OCT images of a FTMH, LMH, and pseudo MH.

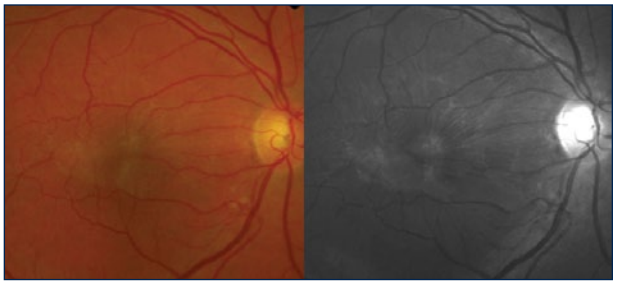

Figure 7. Red-free photographs and blue-reflectance photographs give more details than color fundus photographs.

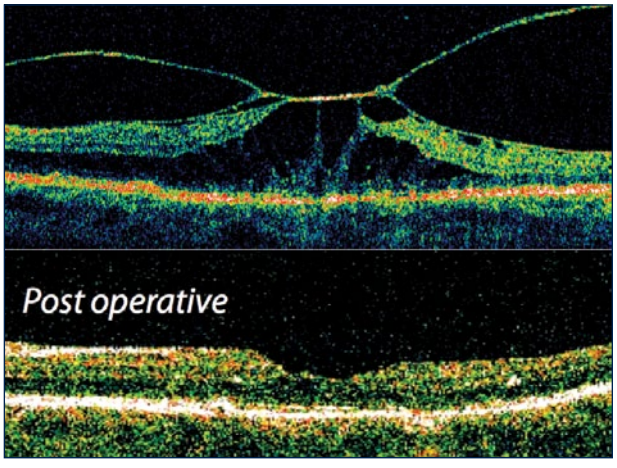

Figure 8. Surgery is often required and gives good functional results if visual acuity at the time of surgery is not too low.

In our experience, surgical intervention for FTMHs between 250 µm and 400 µm is simple and can be performed with small-gauge instrumentation, intraoperative gas in lieu of require postoperative positioning, and does not require peeling of the internal limiting membrane (ILM). In a recent study, we had a 97% success rate performing surgery using these parameters.[5]

Large FTMHs (≥400 µm) have a high risk of nonclosure. For these, we recommend small-gauge surgery with both ERM and ILM peeling and postoperative positioning. Peeling the ILM is an important step for FTMHs larger than 400 µm, as we demonstrated in several studies.[6,7]

Extra-large FTMH (≥800 µm) are generally considered to have a poor prognosis.* There are currently no data available regarding outcomes with surgical intervention, so we performed a study in 2007 in which we operated on 18 extra-large FTMH (810 µm to 1501 µm, mean 942 µm) and compared our results to those from surgeries on large FTMH (400 µm to 800 µm). We had expected to find the rates of closure of the 18 extra-large FTMH to be low but were surprised to find that the closure rate to be 72.2% and the visual acuity in those FTMH that closed increased by a mean of -0.565 Log MAR, which was similar to closure rates and visual acuity gains in the comparison cases (Tadayoni R, unpublished data).

*JETREA® is indicated in adults for the treatment of vitreomacular traction, including when associated with macular hole of diameter less than or equal to 400 µm. Full Prescribing Information for JETREA® can be found on page 20.

NEW DIRECTIONS FOR SPECIFIC VMI DISORDERS

Ocriplasmin was approved by the European Medicines Agency in March 2013 to pharmacologically release adhesion of the vitreous from the macula. This agent offers us a new option that avoids the risks associated with surgery while offering a treatment for for patients with VMT (including when associated with small macular holes) in which we would watch and wait in the past. Based on what we know about ocriplasmin, this represents an excellent alternative for our patients with FTMHs ≤400 µm, VMT without ERM, and/or area of adhesion ≤1500 µm. Pravin U. Dugel, MD's, article on page 13 provides data from the clinical trials and subgroup data, which is critical for the clinician to consider when considering ocriplasmin for their patients. ■

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Patient Selection is Critical for Success With Ocriplasmin

BY PRAVIN U. DUGEL, MD

Ocriplasmin (Jetrea, Alcon) is a truncated form of human plasmin. It is made with recombinant DNA technology and targets degraded extracellular molecules, such as fibronectin, laminin, and collagen, that comprise the macromolecular vitreomacular attachment complex. The mechanism of action of ocriplasmin is to enhance vitreous liquefaction and to facilitate separation of the vitreous cortex from the internal limiting membrane of the retina.[1]

PHASE 3 CLINICAL TRIALS

The phase 3 studies of ocriplasmin, known as the MIVI-TRUST program, consisted of 2 separate trials: TG-MV-006, which was conducted in the United States; and TG-MV-007, which was conducted in the United States and European Union.[2] The trials were prospective, randomized, double-masked, placebo-controlled, and evaluated the efficacy and safety in 652 eyes of a single intravitreal injection of 125 µg ocriplasmin vs placebo for the treatment of patients with symptomatic vitreomacular adhesion (VMA). Importantly, the control arm was a placebo injection (not a sham group). This means the volume effect was negated and only the true drug effect was measured. The study duration was 6 months.

The primary endpoint was nonsurgical resolution of VMA at 28 days as determined by optical coherence tomography (OCT). Secondary endpoints included total posterior vitreous detachment (PVD) at day 28, nonsurgical closure of full-thickness macular hole (FTMH), a gain of 3 or more lines in the assessment of best corrected visual acuity without vitrectomy, need for vitrectomy, and patient-reported assessment of visual function (with the National Eye Institute Visual Functioning Questionnaire-25).

Patients in these trials fell into 3 nonexclusive categories: vitreomacular traction (VMT) without FTMH or epiretinal membrane (ERM) at baseline; FTMH with or without ERM at baseline; and patients with ERM at baseline. All patients were symptomatic and had OCT-confirmed VMA. Ocriplasmin met the studies' primary endpoint of non-surgical resolution of VMA at day 28. In the integrated data analysis of the 2 phase 3 studies, 26.5% of patients in the ocriplasmin group achieved VMA resolution at day 28 compared with 10.1% in the placebo group, a difference that was statistically significant. Ocriplasmin works fairly quickly. Approximately 75% of cases that resolve do so within the first week after injection, and about 100% of cases that resolve do so within the first month.

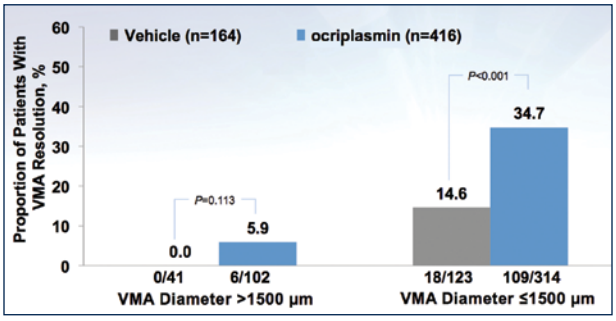

Figure 1. Success of vitreomacular adhesion (VMA) release was significantly higher when the area of adhesion was smaller than 1500 µm (34.7%).

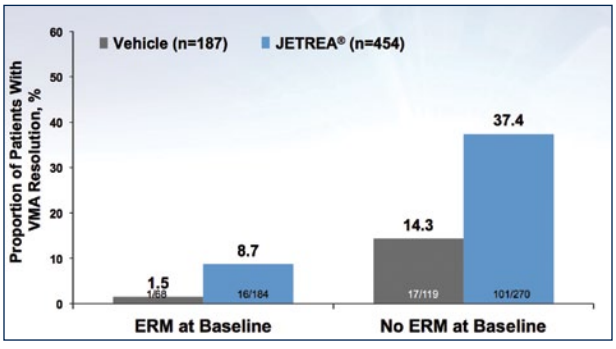

Figure 2. The absence of ERM at baseline was also an indicator of success, with 37.4% of patients without ERM achieving VMA resolution after ocriplasmin injection vs only 8.7% of patients with ERM achieving resolution.

Concerning the secondary endpoint of total PVD at day 28, statistically significant more patients obtained total PVD in the ocriplasmin arm compared to placebo injection, respectively 13.4% and 3.7% ($P < .001$). Nonsurgical closure of FTMH was achieved by 40.6% of patients in the ocriplasmin group at day 28 through month 6.

WHAT WE LEARNED FROM THE CLINICAL TRIALS

It is not rare for a drug post-market to have different success rates compared with the controlled premarket

clinical trials (ie, phase 3 data). The reasons for this are varied, and include complex study designs that are difficult to mimic in a real-world setting, deviation from trial protocol, and patient selection criteria.

The success rate of 26.5%, while statistically significant, can appear disappointing in the context of real-world use of ocriplasmin. However, since the time of the clinical trials, we have had the benefit of understanding which patients are most likely to benefit from enzymatic vitreolysis. As Anselm Kampik, MD, describes in his article on the types of vitreomacular interface (VMI) disorders, there are varying types of disease, and these different diseases of the VMI may respond differently to a particular approach.

USING THE DATA TO SELECT THE RIGHT PATIENTS

A question that may arise is: How can we use the clinical data to improve patient selection to potentially increase the likelihood of success following ocriplasmin injection? Post hoc subgroup analysis on the predictors of response on VMA release has been performed as part of the TG-MV-006 and TG-MV-007 clinical data analyses. From the predictors of response analyzed, the size of the adhesion and the absence of ERM at baseline have shown a positive correlation to VMA release at day 28. The effect of ocriplasmin is reduced in subjects with an ERM or a VMA diameter of >1500 µm at baseline.

From the predictors of response analyzed, the size of the adhesion and the absence of epiretinal membrane at baseline have shown a positive correlation to vitreomacular adhesion release at day 28.

Figure 1 shows that success of VMA release was significantly higher when the area of adhesion was smaller than 1500 µm (34.7%). Additionally, the absence of ERM at baseline was also an indicator of success, with 37.4% of patients without ERM achieving VMA resolution after ocriplasmin injection vs only 8.7% of patients with ERM achieving resolution (Figure 2).

Patients presenting with FTMH at baseline requiring surgery are of special interest of treatment with ocriplasmin to me. Patients who are undergoing surgery will

TABLE 1. THE MOST COMMON AND LESS COMMON ADVERSE EVENTS WITH THE USE OF OCRIPLASMIN FROM THE PHASE 3 CLINICAL TRIALS.

Most Common (5% to 20%)	Less Common (2% to <5%)
Vitreous floaters	Macular edema
Conjunctival hemorrhage	Increased intraocular pressure
Eye pain	Anterior chamber cell
Photopsia	Photophobia
Blurred vision	Vitreous detachment
Macular hole	Ocular discomfort
Reduced visual acuity	Iritis
Visual impairment	Cataract
Retinal edema	Dry eye
	Metamorphopsia
	Conjunctival hyperemia
	Retinal degeneration

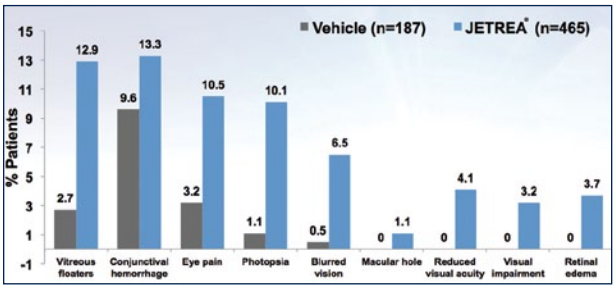

Figure 3. The rate of adverse reactions occurring during the first 7 days following the injection in the ocriplasmin arm is higher than in the placebo arm and most of these common events were related to the mechanism of action of the drug itself, such as flashes, floaters, and photopsia (sudden detachment of the traction and PVD).

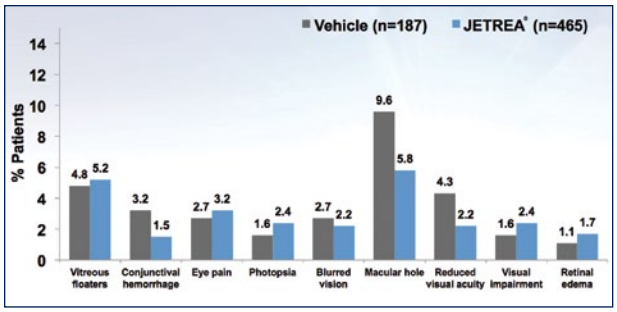

Figure 4. From day 8 until day 180, many of these adverse reactions subsided but their rates were equivalent to placebo.

require time anyway to plan for the surgery and the postoperative positioning, so injecting ocriplasmin a few weeks or so prior to surgery will not make a difference. I schedule all my patients with FTMH who are candidates for ocriplasmin for surgery in 30 days from the time of injection, because by that time, I will know whether the injection worked.

It is critical to remind all patients that ocriplasmin simulates a surgical procedure and that their post-injection vision will most likely decrease initially before it gets better, which is comparable to a postoperative follow-up following an ERM removal or macular hole closure surgeries. If, for example, a patient is 20/50 preoperatively, it is likely that 1 week after surgery he or she will drop to 20/200 vision. The same observation is true for ocriplasmin injection. Vision improvement may be more gradual for some patients, so it is important to educate patients on this matter.

It is critical to remind all patients that ocriplasmin simulates a surgical procedure and that their post-injection vision will most likely decrease initially before it gets better.

TIPS FOR PATIENT MANAGEMENT

Properly prepare your patients—even if they appear to be ideal candidates. Some tips:

- Explain the side effects that may occur in detail, such as flashes, floaters, and transient vision loss
- Provide them with a list of reasons that they should call you (eg, symptoms of retinal detachment vs normal side effect of the drug, endophthalmitis)
- Consider injecting in the morning, so that if the patient is disturbed by postinjection symptoms, he or she may be seen in the afternoon clinic, instead of in the middle of the night
- Make sure they are aware that transient vision loss is a common side effect
- Careful management with ocriplasmin cannot be overstated

SAFETY

The clinical studies provided safety data. Table 1 shows the most common and less common adverse events observed during the pivotal clinical studies.

As is seen in Figures 3 and 4, the rate of adverse reactions occurring during the first 7 days following the injection in the ocriplasmin arm is higher than in the placebo arm and most of these common events were related to the mechanism of action of the drug itself, such as flashes, floaters, and photopsia (sudden detachment of the traction and PVD). From day 8 until day 180, many of these adverse reactions subsided, but their rates were equivalent to placebo.

As indicated above some of the patients injected with ocriplasmin may temporarily lose lines of visual acuity following the weeks after the injection. Thirty-six (7.7% compared to 1.6% with placebo injection) patients lost ≥2 lines of visual acuity at 1 week following injection. Visual acuity decreases were generally reversible within 2 weeks without intervention.

Dyschromatopsia has been reported as a common adverse reaction in patients injected with JETREA in the TG-MV-006 and TG-MV-007 trials. The majority of events were nonserious, mild, and generally resolved spontaneously. The median time to resolution was 3 months.

Electroretinographic (ERG) changes (a- and b-wave amplitude decrease) have been reported as a common adverse reaction in patients injected with ocriplasmin

in the pivotal studies. In the majority of cases, dyschromatopsia was also reported. In approximately half of the cases, the ERG changes had resolved at the time of the last follow-up. The median time to resolution was 6 months. ERG changes were not predictive of negative outcomes in terms of visual acuity.

ERG is systematically evaluated in an ongoing randomized clinical trial with ocriplasmin vs sham, 24-month follow-up, TG-MV-014 (OASIS study; NCT01429441). Results from this trial will provide additional clarifications on the observed ERG changes and dyschomatopsia events reported during the TG-MV-006 and TG-MV-007 trials.

SUMMARY

Post hoc sub-analyses of the clinical trials showed that the absence of ERM or focal adhesions ≤1500 µm at baseline have shown higher rates of VMA release. In that spirit, we looked at the predictors of response in the MIVI TRUST trials. Ocriplasmin is an effective drug for some, but not all, patients. It behooves the clinician to understand these predictors of response, such as absence of ERM at baseline, size of the adhesion, and size of the macular hole. In the patient selection process to ensure a more successful outcome. ■

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Ocriplasmin Case Reports

BY PRAVIN U. DUGEL, MD

TRAPPED FLUID POSTINJECTION?

A 70-year-old American Indian monocular woman who resides at a high altitude in a reservation in Arizona presented to me with visual acuity of 20/60 and symptomatic VMA with a FTMH smaller than 400 µm (Figure 1). Because she had visual loss in her good eye and a fairly small FTMH, I considered her a good candidate for ocriplasmin injection.

The same day postinjection, the patient's visual acuity had dropped to 20/400 and the temporal hyaloid began to separate (Figure 2). As FTMH closed, I could see OCT translucency under the fovea. In my experience, the decreasing volume of this translucency is directly proportional to visual recovery. This OCT translucency may be fluid under the fovea that has been trapped. This is only a presumption. As mentioned the source of this OCT translucency is not yet known. As the fluid resolved (Figures 3 and 4), the visual acuity increased.

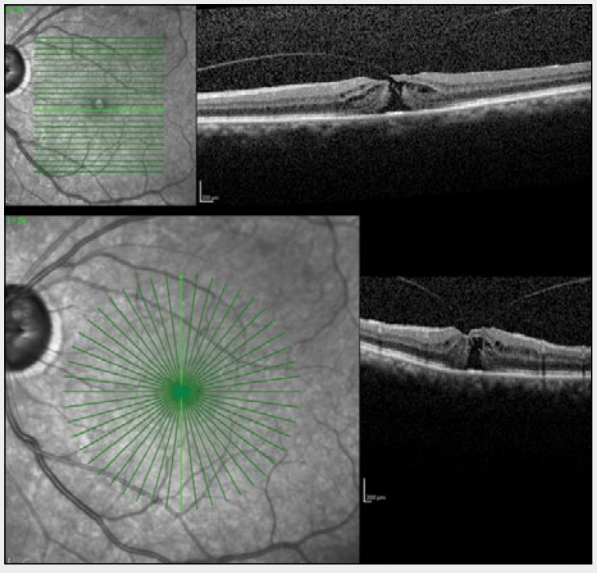

Figure 1 A 70-year-old Native American monocular woman who resides at a high altitude in a reservation in Arizona presented with visual acuity of 20/60 and symptomatic VMA with a small FTMH.

TAKE-HOME POINTS

This is a situation where the patient was not ini-

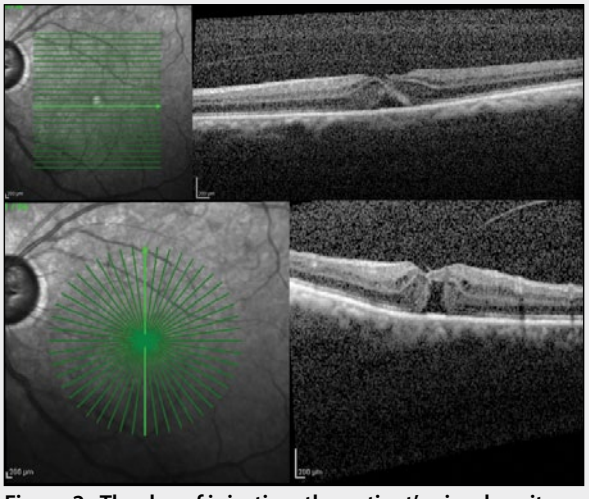

Figure 2. The day of injection, the patient's visual acuity had dropped to 20/400. The temporal hyaloid had begun to separate.

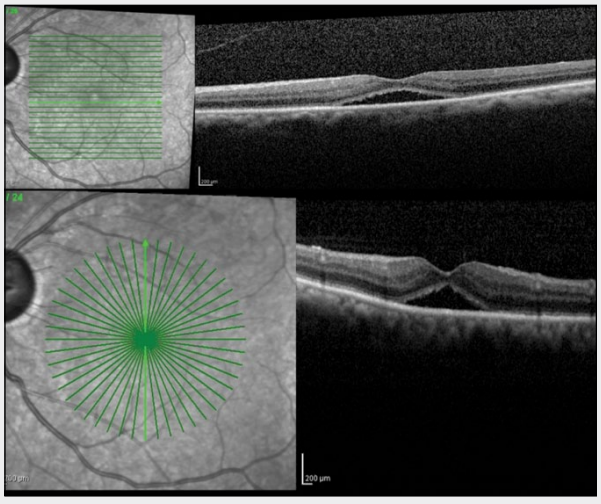

Figure 3. One week post-injection, the patient's visual acuity had improved to 20/80.

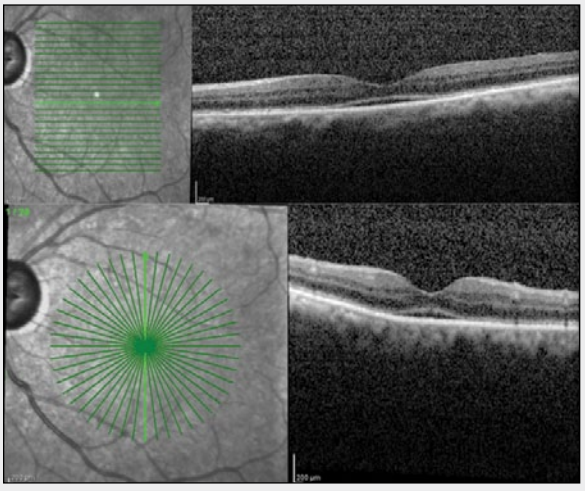

Figure 4. One month after injections, the patient's visual acuity had improved to 20/30.

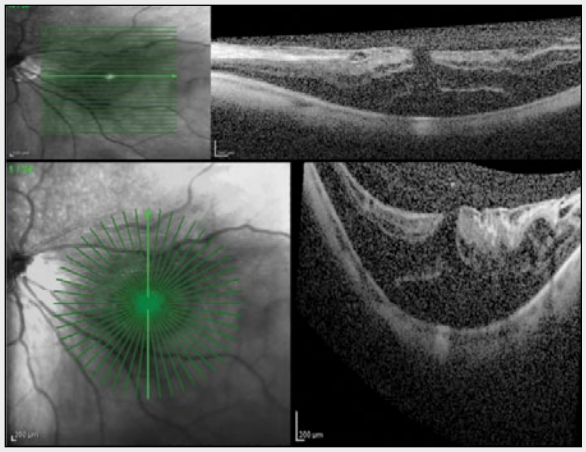

Figure 5. Woman with 20/200 visual acuity for approximately 6 months.

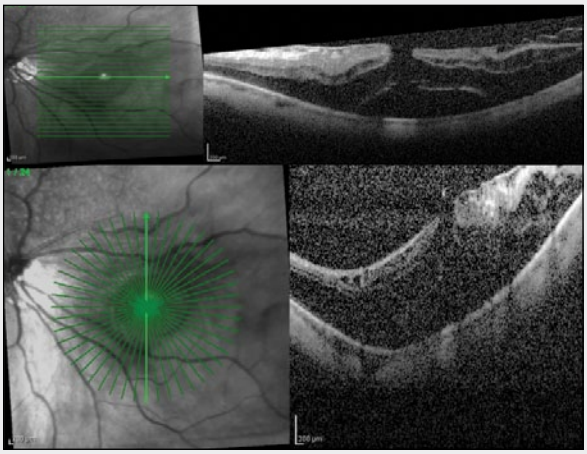

Figure 6. Vision remained at 20/200 the same day after injections with ocriplasmin.

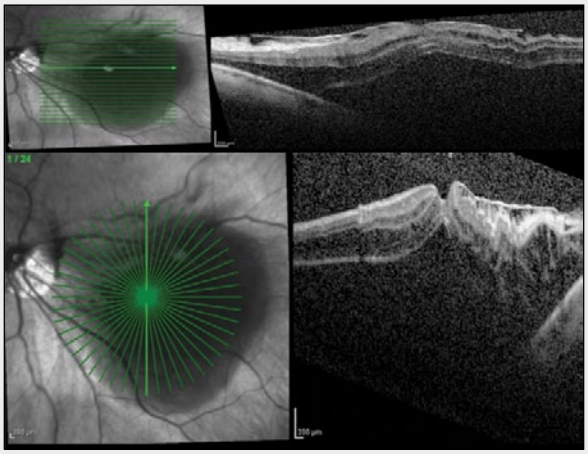

Figure 7. At 1 month post-injection the ERM is further contracting from the retina and the patient is subjectively worse, even thought the visual acuity is the same.

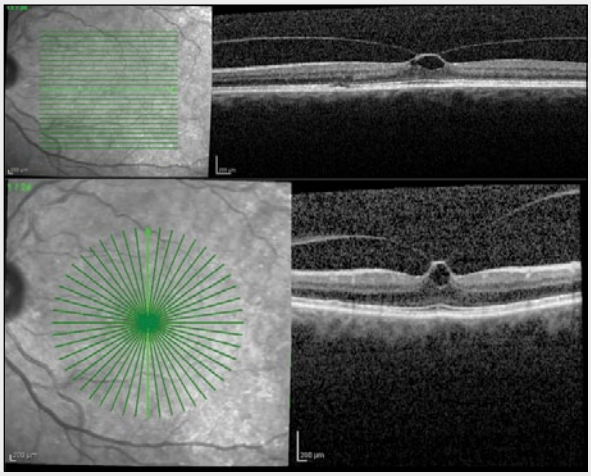

Figure 8. A patient presented with 20/30 vision. She was told that her vision would likely decrease immediately after injection with ocriplasmin, but she insisted that we proceed.

tially happy, even though I was pleased the adhesion had released. It is important to have confidence in the data and to walk your patient through such postinjection experiences. This particular patient still has some fluid remaining, but I am convinced that, from the clinical trial experience, this will resolve over the next few months.

POOR PATIENT SELECTION

A 57-year-old woman who is an attorney travels 2 to 3 times a week via airplane. She presented to me with 20/200 visual acuity that had persisted for 6 months. Her OCT scan and fluorescein angiogram (FA) are seen in Figure 5.

Her myopia would have excluded her from the MIVI trials, in which the upper limit of myopia allowed was -8.00 D.* She was adamant that she wanted me to operate, but she could not have a gas bubble due to the frequent air travel. The adhesion was focal but the area was large, and she also had lattice degeneration, myopic changes, and atrophic holes. In short, this patient was a bad candidate for ocriplasmin. Even after I explained that there was a minimal chance that ocriplasmin would help her, she insisted on having the injection.

Vision remained at 20/200 the same day postinjection (Figure 6) and 1-week postinjection. Her appearance on OCT and FA had not changed either.

One month after injection, the patient's impression was that her condition had worsened, but her visual acuity had not changed. The reason for this was most likely that the elevation of the VMT peripherally that was causing tightening (Figure 7). I was concerned that I was making the FTMH bigger by increasing traction.

This patient did not get better after the injection. I have

*JETREA® has not been studied in patients with high myopia (>8 D spherical correction axial length >28 mm).

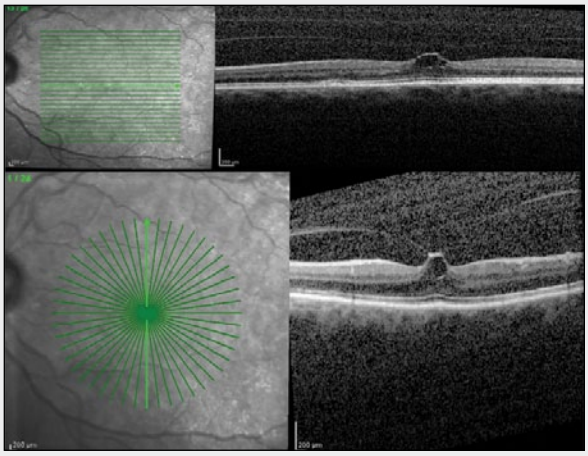

Figure 9. The same day post-injection, her vision had decreased to 20/200.

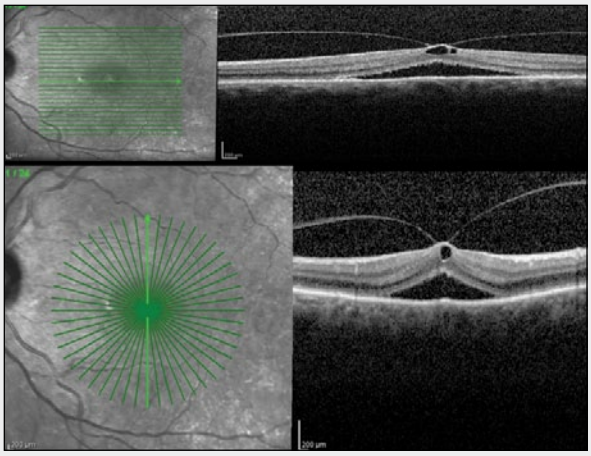

Figure 10. She showed little improvement at 1 week.

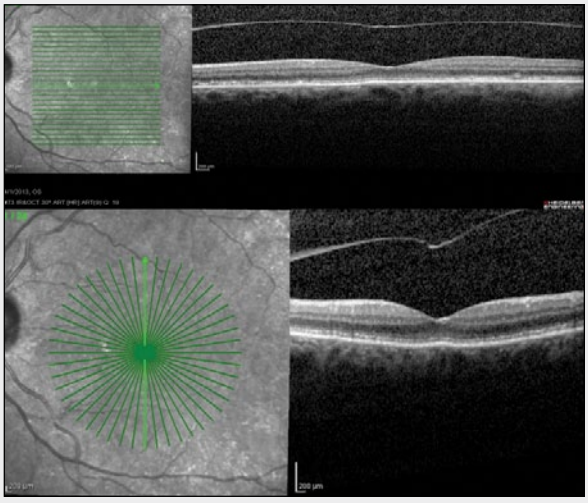

Figure 11. One month later, the patient experienced a complete PVD, and on OCT her retina was completely flat, with complete resolution of the VMT. Her final visual acuity is 20/20

scheduled her for surgery, and although this is a difficult case, I am hopeful she will do well.

TAKE-HOME POINTS

This was a case of bad patient selection. This patient was well outside the guidelines for patient selection and I should not have let her convince me to inject. Moreover, the pathophysiology of myopic macular schisis and subsequent macular hole formation is entirely different.

THE "CEMENTED" VMA

The next case is that of a 73-year-old woman. She presented complaining of issues with her color vision. She had bilateral VMT and symptoms that had persisted for 4 years (I had been following this patient for 2 years). This was a particularly exacting patient who had sought out alternative therapies for vision problems, including extreme yoga and inversion therapy.

Her vision was 20/30 in her worse eye (Figure 8) and 20/20 in her better eye.

I was uncertain as to why the adhesion had not released in 4 years but was aware that, although they are uncommon, some patients do not resolve. I informed the patient that the vision would likely decrease after injection, but she wanted to proceed. The same day after injection, her vision decreased, as predicted, to 20/200 (Figure 9). At week 1 postinjection, she showed little improvement (Figure 10) but I wanted to wait at least 1 month before scheduling her for surgery.

One month later, she called me in a panic from London. She planned to fly directly home to see me. I immediately thought that she had a retinal detachment or something worse. When I examined her and reviewed her OCT, there was complete resolution of VMT (Figure 11). I can only guess that the adhesion released rapidly and this startled her. The patient's vision is now 20/20 and she is happy.

Patient counseling prior to the injection [of ocriplasmin], including possible side effects is critical in managing expectations.

TAKE-HOME POINTS

Sometimes it is difficult to predict what will happen, even in patients who appear to be perfect candidates for ocriplasmin. There may a subgroup of patients who have a "cemented" VMA that will not release spontaneously. Patient counseling prior to the injection, including possible side effects is critical in managing expectations.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

JETREA 0.5 mg/0.2 ml concentrate for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 0.5 mg of ocriplasmin* in 0.2 ml solution.
After dilution with 0.2 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, 0.1 ml of the diluted solution contains 0.125 mg ocriplasmin.

*Ocriplasmin is a truncated form of human plasmin produced by recombinant DNA technology in a *Pichia pastoris* expression system.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection (sterile concentrate).
Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

JETREA is indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns (see section 5.1).

4.2. Posology and method of administration

JETREA must be prepared and administered by a qualified ophthalmologist experienced in intravitreal injections. The diagnosis of vitreomacular traction (VMT) should comprise of a complete clinical picture including patient history, clinical examination and investigation using currently accepted diagnostic tools, such as optical coherence tomography (OCT).

Posology
The recommended dose is 0.125 mg (0.1 ml of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose. Each vial should only be used once and for the treatment of a single eye. Treatment with JETREA in the other eye is not recommended concurrently or within 7 days of the initial injection in order to monitor the post-injection course including the potential for decreased vision in the injected eye. Repeated administration in the same eye is not recommended (see section 4.4).

See section 4.4 for instructions on post-injection monitoring.

Special populations
Renal impairment
No formal studies have been conducted with JETREA in patients with renal impairment. No dose adjustment or special considerations are anticipated for patients with renal impairment (see section 5.2).

Hepatic impairment
No formal studies have been conducted with JETREA in patients with hepatic impairment. No dose adjustment or special considerations are anticipated for patients with hepatic impairment (see section 5.2).

Elderly
The elderly population has been studied in clinical studies. No dose adjustment is required.

Paediatric population
There is no relevant use of JETREA in children aged under 18 years in vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns. Currently available data on paediatric use are described in section 5.1.

Ethnicity
Experience is limited in groups other than Caucasians.

Method of administration
Single use vial for intravitreal use only.

Preoperative antibiotic drops may be administered at the discretion of the treating ophthalmologist.

Precautions to be taken before handling or administering the medicinal product
The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of surgical hand disinfection, sterile gloves, a sterile drape, a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad spectrum topical microbiocide should be administered prior to the injection according to standard medical practice.

For instructions on dilution of the medicinal product before administration, see section 6.6.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus aiming towards the centre of the vitreous cavity avoiding the horizontal meridian. The injection volume of 0.1 ml is then delivered into the mid-vitreous.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active or suspected ocular or periocular infections.

4.4. Special warnings and precautions for use

Post-injection monitoring
JETREA is administered by intravitreal injection only. Intravitreal injections have been associated with intraocular inflammation/infection, intraocular haemorrhage and increased intraocular pressure (IOP). Proper aseptic injection techniques must always be used. Following the intravitreal injection, patients should be monitored for any side effects such as (but not limited to) intraocular inflammation/infection and elevation in IOP. Transient increases in IOP including transient blindness and non-perfusion of the optic nerve have been seen within 60 minutes of injection of JETREA. Monitoring for increases in IOP may consist of a check for perfusion of the optic nerve head immediately after the injection and tonometry within 30 minutes following the injection. Intraocular inflammation/infection may be assessed using biomicroscopy between 2 and 7 days following the injection. Patients should be instructed to report symptoms suggestive of intraocular inflammation/infection or any other visual or ocular symptoms without delay. If any of the above events occur the patient should be treated according to standard medical practice.

Other warnings and precautions
The safety and efficacy of JETREA administered to both eyes concurrently has not been studied. Therefore administration to both eyes concurrently is not recommended.

Repeated administration of JETREA in the same eye has not been adequately studied and is therefore not recommended.

There are no clinical data on concomitant use of ocriplasmin with VEGF-inhibitors.

JETREA has not been studied in patients with large diameter macular holes (> 400 microns), high myopia (> 8 dioptre spherical correction or axial length > 28 mm), aphakia, history of rhegmatogenous retinal detachment, lens zonule instability, recent ocular surgery or intraocular injection (including laser therapy), proliferative diabetic retinopathy, ischaemic retinopathies, retinal vein occlusions, exudative age-related macular degeneration (AMD) and vitreous haemorrhage. Treatment is not recommended in such patients.

The potential for lens subluxation or phacodonesis cannot be ruled out (see section 4.8 and 5.3).

There is limited experience in patients with non-proliferative diabetic retinopathy or history of uveitis (including active severe inflammation) or significant eye trauma. Caution should be exercised when treating such patients.

The effect of ocriplasmin (particularly in inducing resolution of vitreomacular adhesion or causing total posterior vitreous detachment [PVD]) is reduced in subjects with an epiretinal membrane (ERM) or a diameter of VMA > 1500 microns (see section 5.1).

Due to a potential increase in tractional forces, there is a risk of occurrence of new or enlarged macular holes (see section 4.8).

There is a risk for a significant, but transient loss of visual acuity during the first week after the injection. Patients should be monitored appropriately (see section 4.8).

4.5. Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

Ocriplasmin is a proteolytic enzyme with serine protease activity which could be present in the eye for several days after intravitreal injection (see section 5.2). Administration in close temporal association with other medicinal products in the same eye may affect the activity of both medicinal products and is therefore not recommended.

No systemic interactions are anticipated.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no data for the use of JETREA in pregnant women. No reproductive toxicology studies have been performed. The systemic exposure of JETREA is expected to be very low after intravitreal injection. JETREA should be used during pregnancy only if the clinical benefit outweighs the potential risks.

Breast-feeding
It is unknown whether JETREA is excreted in human milk. JETREA should be used during breast-feeding only if the clinical benefit outweighs the potential risks.

Fertility
There are no data on the effect of JETREA on fertility.

4.7. Effects on ability to drive and use machines

The intravitreal injection of JETREA may be followed by temporary visual disturbances (see section 4.8). In these cases, patients should not drive or use machines until the visual disturbances have resolved.

4.8. Undesirable effects

Summary of the safety profile
Over 800 patients have been treated with an intravitreal injection of JETREA, with over 570 patients treated with the recommended dose of 0.125 mg.

All adverse reactions were ocular. The most commonly reported were vitreous floaters, eye pain and photopsia, as well as conjunctival haemorrhage resulting from the injection procedure. Most of the adverse reactions occurred within the first week after the injection. The majority of these reactions were non-serious, mild in intensity and resolved within 2 to 3 weeks.

The incidence of serious adverse reactions that occurred in all clinical studies was 2.2% in JETREA treated patients and 2.4% in control patients.

Tabulated list of adverse reactions
The following table summarises the adverse reactions that occurredin clinical studies with a reasonable possibility of causality to the injection procedure or JETREA.

The adverse reactions are listed by MedDRA system organ class and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing clinical importance.

Eye disorders	Very common Vitreous floaters, eye pain, conjunctival haemorrhage Common Visual acuity reduced*, visual impairment, vision blurred, retinal haemorrhage, vitreous haemorrhage, retinal tear*, retinal detachment*, intraocular pressure increased, macular hole*, macular degeneration, retinal degeneration, macular oedema, retinal oedema, retinal pigment epitheliopathy, metamorphopsia, vitreous adhesions*, conjunctival oedema, eyelid oedema, vitritis, anterior chamber cell, anterior chamber flare, iritis, photopsia, conjunctival hyperaemia, ocular hyperaemia, vitreous detachment, retinogram abnormal*, eye irritation, dry eye, foreign body sensation in eyes, eye pruritus, ocular discomfort, photophobia, chromatopsia* Uncommon Transient blindness, lens subluxation*, scotoma, visual field defect, diplopia, hyphaema, miosis, pupils unequal, corneal abrasion, anterior chamber inflammation, eye inflammation, conjunctival irritation
* see section 'Description of selected adverse reactions'	

Description of selected adverse reactions
Visual acuity reduced
In the placebo-controlled pivotal phase III studies, 7.7% of JETREA patients and 1.6% of placebo patients had acute transient ≥ 2-line (≥ 10 ETDRS letters) loss in best corrected visual acuity (BCVA) during the first week after injection with no alternative explanation for the change. Visual acuity decreases were generally reversible within 2 weeks without intervention. See section 4.4 for monitoring recommendations.

Chromatopsia
Dyschromatopsia (generally described as yellowish vision) has been reported as a common adverse reaction in patients injected with JETREA. The majority of events were non-serious, mild and generally resolved spontaneously. The median time to resolution was 3 months.

Retinogram abnormal
Electroretinographic (ERG) changes (a- and b-wave amplitude decrease) have been reported as a common adverse reaction in patients injected with JETREA; in the majority of cases dyschromatopsia was also reported. In approximately half of the cases, the ERG changes had resolved at the time of the last follow-up. The median time to resolution was 6 months. ERG changes were not predictive of negative outcomes in terms of visual acuity.

Retinal breaks (tears and detachment)
In the placebo-controlled pivotal phase III studies, retinal breaks (tears and detachment) were reported in 1.9% of patients injected with JETREA vs. 4.3% injected with placebo. Most of these events occurred during or after vitrectomy in both groups. The incidence of retinal detachment that occurred pre-vitrectomy was 0.4% in the JETREA group and none in the placebo group, while the incidence of retinal tears (without detachment) that occurred pre-vitrectomy was 0.2% in the JETREA group and 0.5% in the placebo group.

Macular hole
In the placebo-controlled pivotal phase III studies, cases of new onset or worsening of macular hole were reported for 6.7% of all patients injected with JETREA vs. 9.6% injected with placebo. Although in placebo-controlled pivotal phase III studies, JETREA has shown benefit in inducing closure of macular holes associated with vitreomacular traction, in some instances increased traction with subsequent progression or development of new macular hole has been observed. Development of these events is part of natural disease progression; however, a contribution of ocriplasmin in some cases appears plausible based upon its mechanism of action.

Vitreous adhesions
In the placebo-controlled pivotal phase III studies, cases of worsening of vitreomacular adhesion/vitreomacular traction were reported for 1.5% of all patients injected with JETREA vs. 1.1% injected with placebo. Development of these events is part of natural disease progression; however, a contribution of ocriplasmin in some cases appears plausible based upon its mechanism of action.

Lens subluxation/phacodonesis
One case of lens subluxation/phacodonesis was reported in clinical studies in adults and appears to have been possibly related to treatment with JETREA. In a paediatric study evaluating JETREA as an adjunct to vitrectomy, one case of subluxation was reported in a premature infant who received a single intravitreal injection of JETREA 0.175 mg. Lens subluxation was observed in 3 animal species at ocriplasmin concentrations above the intended clinical concentration (see section 5.3).

Based on the proteolytic activity of ocriplasmin, preclinical and clinical findings, the potential for lens subluxation or phacodonesis cannot be ruled out. If this event occurs, it should be treated according to standard medical practice.

See section 4.4 for monitoring recommendations. Routine observation is recommended in all above situations.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9. Overdose

The clinical data on the effects of JETREA overdose are limited. One case of accidental overdose of 0.250 mg ocriplasmin (twice the recommended dose) has been reported. The patient had a decrease in BCVA of 21 ETDRS letters from baseline that returned to within 9 letters of baseline at the end of the study. The patient also developed mild conjunctival hyperaemia, eye inflammation and miosis which resolved with corticosteroid eye drops.

If an overdose occurs, close monitoring is recommended. If an adverse reaction occurs, it should be treated according to standard medical practice.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, Other ophthalmologicals, ATC code: S01XA22

Mechanism of action
Ocriplasmin has a proteolytic activity against protein components of the vitreous body and the vitreoretinal interface (VRI) (e.g. laminin, fibronectin and collagen) and aims to dissolve the protein matrix responsible for the abnormal vitreomacular adhesion (VMA). The tight binding of the protein components within the macular area of the VRI contribute to vitreomacular traction (VMT), leading to visual impairment and/or macular holes.

Clinical efficacy and safety
The efficacy of JETREA was demonstrated in 2 multicentre, randomised, double-masked, placebo-controlled, 6-month studies in patients with VMT. A total of 652 patients (JETREA 464, placebo 188) were randomised in these 2 studies (TG-MV-006 and TG-MV-007).

In both pivotal studies, the proportion of patients who achieved VMA resolution at Day 28 (primary endpoint) was significantly (p≤0.003) higher in the JETREA group compared with the placebo group. The difference continued to be statistically significant through Month 6 in each study (p≤0.024). In the integrated data, 26.5% in the JETREA group compared with 10.1% in the placebo group achieved VMA resolution at Day 28 (p<0.001). The difference was maintained from Day 7 through Month 6 (Figure 1).

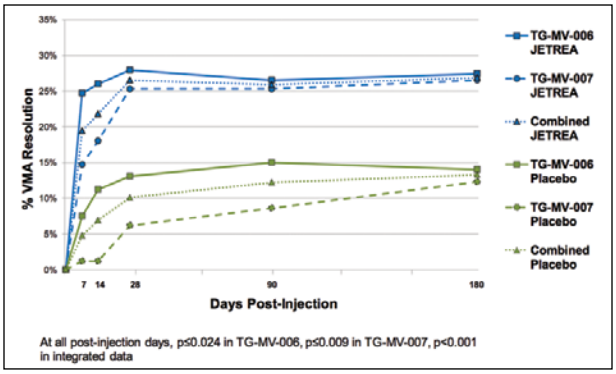

Figure 1: Proportion of patients with VMA resolution up to Day 180 (Month 6) (TG-MV-006, TG-MV-007 and integrated data)

Patients with no ERM at baseline were more likely to achieve VMA resolution at Day 28 compared with those who had ERM at baseline. In the integrated data, the VMA resolution rate at Day 28 was higher in patients treated with JETREA compared to placebo in both the subgroup without ERM (37.4% vs. 14.3%, p<0.001) and with ERM (8.7% vs. 1.5%, p=0.046).

Patients with a smaller VMA diameter at baseline (≤ 1500 microns) were more likely to achieve VMA resolution at Day 28 compared with those who had a diameter > 1500 microns. In the integrated data, the VMA resolution rate at Day 28 was higher in patients treated with JETREA compared to placebo in both the subgroup with VMA ≤ 1500 microns at baseline (34.7% vs. 14.6%, p<0.001) and with VMA > 1500 microns at baseline (5.9% vs. 0%, p=0.113).

In the integrated data, 106 (22.8%) and 47 (25%) in the JETREA and placebo groups respectively had full thickness macular hole (FTMH) at baseline. Of these, the proportion of patients who achieved FTMH closure without vitrectomy at Day 28 was higher in the JETREA group than the placebo group (40.6% vs. 10.6%, respectively; p<0.001). A difference was maintained through the end of the studies (Month 6).

A significantly higher percentage of JETREA treated patients experienced total PVD at Day 28 compared to placebo treated patients (integrated data: 13.4% vs. 3.7%, respectively; p<0.001).

During the studies, vitrectomy could be performed at the discretion of the Investigator. JETREA treated patients were less likely to have had a vitrectomy by the end of the study (Month 6) compared with placebo treated patients (integrated data: 17.7% vs. 26.6%, respectively; p=0.016).

A higher proportion of JETREA treated patients gained ≥ 2 or ≥ 3 lines in BCVA (irrespective of vitrectomy) at Month 6 (28.0% and 12.3%, respectively) compared with patients treated with placebo (17.1% and 6.4%) (p=0.003 and p=0.024, respectively). Also the proportion of patients gaining ≥ 2 or ≥ 3 lines in BCVA without vitrectomy favoured JETREA at Month 6 (23.7% vs. 11.2%, p<0.001 for a gain ≥ 2 lines and 9.7% vs. 3.7%, p=0.008 for a gain ≥ 3 lines).

In the integrated analysis of the National Eye Institute Visual Function Questionnaire-25 (VFQ-25), a numerical favour of JETREA over placebo was shown in each sub-scale score, as well as the composite score. The difference for improvement in the general vision sub-scale score was statistically significant (6.1 JETREA vs. 2.1 placebo, p=0.024).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with JETREA in all subsets of the paediatric population in the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns (see section 4.2 for information on paediatric use).

The safety and efficacy of ocriplasmin in paediatric subjects scheduled for vitrectomy was investigated in study TG-MV-009. A single intravitreal injection of 0.175 mg (above the recommended dose), or placebo, was injected in the mid-vitreous of 24 eyes of children aged 0 to 16 years, 30 to 60 minutes prior to the planned start of vitrectomy. The main reasons for vitrectomy were retinal detachment and retinopathy of prematurity. Treatment with ocriplasmin did not demonstrate an effect on posterior vitreous detachment rate, vitreous liquefaction grade, immediate postoperative retinal reattachment rate, development of proliferative vitreoretinopathy, or stage of retinopathy of prematurity. The safety findings observed in study TG-MV-009 were consistent with the known safety profile for JETREA. Based on the results of this study, the use of JETREA as an adjunct to vitrectomy in children, to facilitate vitreous separation and removal, is not recommended.

5.2. Pharmacokinetic properties

Ocriplasmin levels in the vitreous decrease rapidly after intravitreal administration. In a clinical study in patients scheduled for vitrectomy receiving 0.125 mg JETREA (corresponding to a theoretical start concentration of 29 µg/ml vitreous), mean ocriplasmin activity was 9% of theoretical start concentration 2-4 hours after injection and below the lower level of quantification at 7 days.

Because of the small dose administered (0.125 mg), detectable levels of ocriplasmin in systemic circulation are not expected after intravitreal injection.

When administered intravenously, ocriplasmin enters the endogenous protein catabolism pathway through which it is rapidly inactivated via its interactions with protease inhibitor α2-antiplasmin or α2-macroglobulin. The inactive ocriplasmin/α2-antiplasmin complex is cleared from the circulation with a half-life (t1/2) of several hours.

Renal impairment
No studies have been conducted to examine the pharmacokinetics of ocriplasmin in patients with renal impairment since the systemic exposure is expected to be very low after intravitreal administration.

Hepatic impairment
No studies have been conducted to examine the pharmacokinetics of ocriplasmin in patients with hepatic impairment since the systemic exposure is expected to be very low after intravitreal administration.

5.3. Preclinical safety data

The intravitreal toxicity of ocriplasmin has been evaluated in rabbits, monkeys and minipigs. Ocriplasmin induced an inflammatory response and transient ERG changes in rabbits and monkeys, while no inflammation or ERG changes were observed in minipigs. In rabbits and monkeys, the incidence of vitreous cell infiltrates tended to resolve over time. In monkeys, after administration of 125 µg/eye (68 µg/ml vitreous) the ERG was fully recovered by Day 55. Lens subluxation was observed in the 3 species at ocriplasmin concentrations at or above 41 µg/ml vitreous, a concentration above the intended clinical concentration of 29 µg/ml. This effect appeared to be dose-related and was observed in all animals administered intravitreal ocriplasmin more than once. Pathological changes related to intraocular haemorrhage were observed in rabbits and monkeys. It remains unclear if this haemorrhage is related to the injection procedure itself or administration of ocriplasmin. No systemic toxicity was observed after intravitreal administration of ocriplasmin.

The systemic toxicity of ocriplasmin has been evaluated in both rat and dog. Intravenous administration of 10 mg/kg was generally well tolerated in both rat and dog whether administered as single dose or as repeated dose.

No carcinogenicity, mutagenicity or reproductive and developmental toxicity data are available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol
Citric acid
Sodium hydroxide (pH adjustment)
Water for injections

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, other than sterile, preservative-free, non-buffered diluent sodium chloride 9 mg/ml (0.9%) solution for injection.

6.3. Shelf life

18 months

After dilution:
From a microbiological point of view, the product should be used immediately. The vial and any unused portion of the diluted solution should be discarded after single use.

6.4. Special precautions for storage

Store in a freezer (-20˚C ±5°C). If the product is exposed to higher temperatures during storage, the vial should be discarded.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5. Nature and contents of container

0.2 ml solution in a vial (type I glass) closed with a latex-free chlorobutyl rubber stopper. Pack containing 1 vial.

6.6. Special precautions for disposal and other handling

Vials are for single use only.

To prepare JETREA for intravitreal injection, adhere to the following instructions:

1. Remove the vial from the freezer and allow to thaw at room temperature (takes about 2 minutes).
2. Once completely thawed, remove the protective polypropylene flip-off cap from the vial.
3. Disinfect the top of the vial with an alcohol wipe.
4. Using aseptic technique, dilute by adding 0.2 ml of sodium chloride 9 mg/ml (0.9%) solution for injection (sterile, preservative-free, non-buffered) into the JETREA vial and gently swirl the vial until the solutions are mixed. The diluent should be withdrawn from an unopened container which should be used only once. The remaining sodium chloride 9 mg/ml (0.9%) solution for injection should be discarded. The diluted solution should be used immediately as it contains no preservatives.
5. Visually inspect the vial for particulate matter. Only a clear, colourless solution without visible particles should be used.
6. Using aseptic technique, withdraw all of the diluted solution using an appropriate sterile needle (slightly incline the vial to ease withdrawal) and discard the needle after withdrawal of the vial contents. Do not use this needle for the intravitreal injection.
7. Replace the needle with an appropriate sterile needle, carefully expel the air from the syringe and adjust the dose to the 0.1 ml mark on the syringe (corresponding to 0.125 mg ocriplasmin).
8. Inject 0.1 ml of the diluted solution immediately into the mid-vitreous as it contains no preservatives.
9. Discard the vial and any unused portion of the diluted solution after single use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ThromboGenics NV
Gaston Geenslaan 1
B-3001 Leuven
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/13/819/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 March 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

RETINA TODAY