Targeting the Underlying Causes of Retinal Disease

Potential applications for enzymatic manipulation of the vitreous.

BY MICHAEL TRESE, MD

Scientists and physicians are increasing their understanding of the vitreous and the role it plays in vitreoretinal pathologies. It is known that the vitreous is a gel-like structure at birth and the aging eye naturally passes through a remodeling of the vitreous, during which it progressively liquefies and often separates from the retina, resulting in posterior vitreous detachment (PVD). However, in some cases there remains an area of attachment at the macula, resulting in vitreomacular adhesion (VMA). When these areas of adhesion cause traction, patients can experience symptoms such as metamorphopsia, deteriorating visual acuity, and formation of macular hole. VMA has also been associated with age-related macular degeneration, retinal vein occlusions, and diabetic macular edema.[1,2]

Until now, VMA and macular holes have been treated either with watchful waiting or, when symptoms become advanced enough to merit the risks, with surgery. Usual surgical management involves a 3-port pars plana vitrectomy to mechanically separate the vitreous from the retina. Ocriplasmin (Jetrea; Thrombogenics), a pharmacologic agent that can produce enzymatic vitreolysis, may finally provide another treatment option. Ocriplasmin is a truncated form of human plasmin with properties that hydrolyze fibronectin, collagen, and laminin in the vitreous, and can induce liquefaction and separation of the vitreous.[3]

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PIVOTAL STUDIES FOR OCRIPLASMIN

Ocriplasmin was studied in 2 pivotal phase 3 clinical trials as a single intravitreal injection for treatment of patients with symptomatic VMA and associated macular hole.[4] The primary endpoint was resolution of VMA at day 28. Secondary endpoints included total PVD at day 28, nonsurgical closure of macular hole, and change in best corrected visual acuity (BCVA). Patients with symptomatic VMA in the United States and Europe given a single injection of 125 µg ocriplasmin (100 µL) were compared to a group given a single placebo injection (100 µL). By day 28, 26.5% of the ocriplasmin group (n=464) achieved resolution of VMA, compared with 10.1% of the placebo group (n=188; $P < .001$). Nonsurgical closure of macular hole occurred in 40.6% of ocriplasmin-injected eyes compared with 10.6% of the placebo group ($P < .001$). For the subset of patients with a macular hole of less than 400 µm (n=86), approximately half (48.8%) of the ocriplasmin patients achieved closure. Complete PVD at day 28 occurred in 13.4% of eyes injected with ocriplasmin and 3.7% of eyes injected with placebo ($P < .001$). Visual acuity and visual function outcomes also favored the ocriplasmin group, with BCVA more likely to improve by at least 3 lines compared with placebo-treated eyes.

Early intervention in cases of symptomatic VMA may be advantageous in limiting the deterioration of visual acuity, visual function, and retinal structure. The phase 3 studies also showed that ocriplasmin is fast-acting; roughly 70% of eyes that achieved resolution of focal VMA at day 28 or macular hole closure had already resolved by day 7. Thus, ocriplasmin can be used as a first-line therapy and will not delay further treatment if it is required.

Most adverse events were considered mild and were transient or temporary in nature, with a majority occur-

ring within the first 7 days after treatment. Vitreous floaters were the most common ocular adverse event, reported by 16.8% of patients in the ocriplasmin-treated group compared with 7.5% in the placebo-treated group (P = .002). This difference can be attributed to the acute events known to be associated with vitreous detachment, as the incidence of vitreous floaters dropped to 3.9% in the ocriplasmin-injected group and 4.8% in the placebo group from day 8 to the end of the study. Patients have reported experiencing bright flashing lights and the appearance of abstract shapes, with their eyes closed as well as open, for the few days during which the vitreous was detaching. The incidence of serious ocular adverse events, which included macular holes, retinal detachments, and reduced visual acuity, was 7.7% in the ocriplasmin-treated group compared with 10.7% in the placebo-treated group (P = .26).

POTENTIAL APPLICATIONS FOR ENZYMATIC MANIPULATION OF THE VITREOUS

Pharmacologic vitreolysis offers a new treatment modality for a variety of vitreoretinal conditions, and it may also be useful as a surgical adjunct. Use of ocriplasmin to facilitate complete PVD may decrease operating time and allow the use of smaller-gauge instruments, thereby reducing many of the risks associated with vitrectomy surgery. As physicians gain more experience with ocriplasmin and its potential, they will continue to define clinical applications for it. Following are some potential applications.

Age-related macular degeneration. Biochemical changes in the vitreous, called pharmacologic vitreodynamics, may be important in the pathogenesis and management of macular diseases, including age-related macular degeneration (AMD). It has been suggested that chronic tractional forces resulting from posterior VMA may antagonize the effects of anti-VEGF treatment, resulting in poor response and inferior visual outcomes.[5] Animal studies show that PVD alters the oxygen and reduces VEGF in the vitreous cavity.[6] This leads to rapid early penetration of anti-VEGF drugs (Figure 1). It is a logical conclusion that achieving PVD may reduce the required dosing of anti-VEGF drugs, steroids, and antibiotics, and improve visual outcomes.

Diabetic macular edema. Ocriplasmin could prove useful in patients with diabetes to separate the vitreous from the retina. VMA and traction of the vitreous cortex are believed to contribute to the pathogenesis of diabetic macular edema (DME) by inducing chronic low-grade inflammation.[7] Resolution of the VMA may reduce the chance of the patient developing very severe retinal changes from DME.

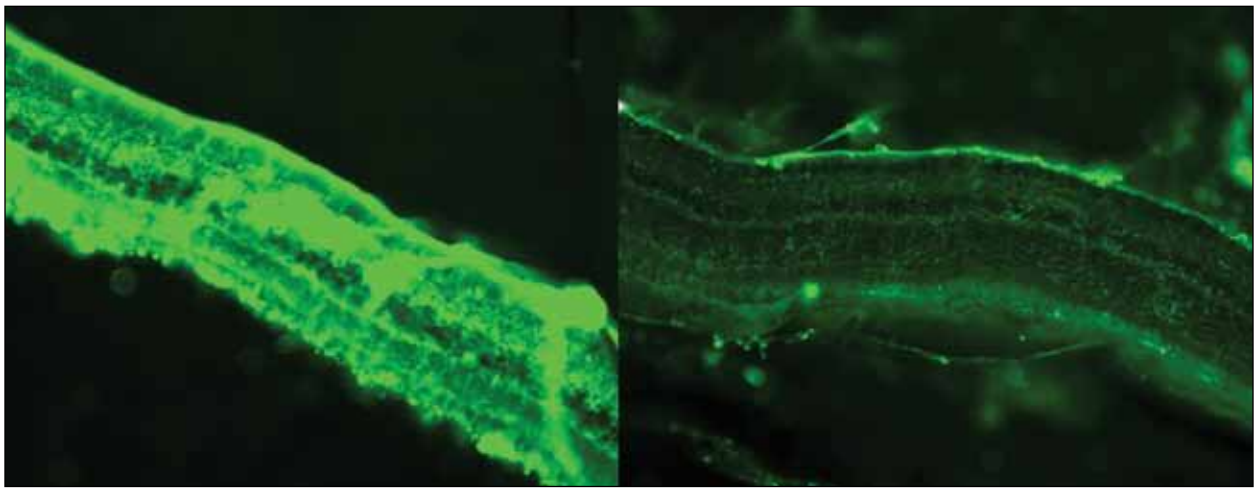

Figure 1. Posterior vitreous detachment leads to rapid early penetration of bevacizumab at 6 hours.

Surgical adjunct. Another possible use for ocriplasmin would be in eyes in which the vitreous is difficult to remove, such as in babies, children, and young adults. Liquefaction allows optimization of small-gauge vitrectomy and could eliminate the need for internal limiting membrane peeling. This could potentially reduce complications of surgery and improve patient recovery.

IMPROVING INJECTIONS

As studies advance the understanding of the vitreous, we are also learning more about how intravitreal injections should be performed. It has been assumed that an injection into the vitreous cavity diffuses equally. However, in an eye in which the vitreous has not been removed, there are canals, areas of solid collagen, and areas of liquid vitreous, all of which change with age. Thus, a substance that is injected into the middle vitreous cavity does not necessarily diffuse as it might in a purely liquid, homogeneous filling.

This is true of all molecules, but in particular for enzymes. Diffusion of enzymatic protein through a macromolecular gel is not like diffusion through water, despite a high water content. Enzymes seem to curtail activity in 2 circumstances. First, they either bind to a substance right away, or they auto-digest. This makes simultaneous injections or injections of a larger quantity of enzyme less effective. Data are emerging that suggest that although ocriplasmin has greater ability to diffuse in the vitreous than plasmin, efficacy is greatest where the enzyme leaves the needle.[8] If an enzyme is injected on 1 side of the vitreous, it works very well in that location. In the middle of the vitreous, however, the enzyme has variable activity, and on the other side of the vitreous it has little to no effect. Thus, the first step in increasing the efficacy of an enzyme injection is to carefully consider the desired focus of action vs where the enzyme is being injected.

We have learned that traction caused by VMA is the underlying pathology of an eye disease called symptomatic VMA, and there is evidence that it contributes to a number of other retinal pathologies. Using ocriplasmin to achieve enzymatic manipulation of the vitreous core and the vitreoretinal junction would provide a much-needed therapeutic alternative to vitrectomy. Continuing research is necessary to define all of the potential applications of enzymatic manipulation of the vitreous. The ability to resolve VMA without surgery should prove to be of great benefit to physicians and, most important, to patients. ■

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