

Management and Intervention Strategies for Symptomatic Vitreomacular Adhesions

Wanted: options to replace “watchful waiting.”

Peter Stalmans, MD, PhD

The vitreous cavity is filled with a gel-type substance comprised of 99% water, with the remaining 1% a network of collagen fibrils, large molecules of hyaluronic acid, hyalocytes, inorganic salts, organic lipids and polysaccharide components.¹ The posterior vitreous cortex, which consists primarily of hyaluronic acid and collagen, is a combination of collagen fibrils and polysaccharides and this matrix forms a biochemical attachment to the ILM.

A normal course for the aging eye involves liquefaction of the vitreous. Liquefaction, although normal, is a complex course of action consisting of two distinct processes: syneresis and synchysis. Complete vitreous separation (syneresis) must occur prior to complete vitreous liquefaction (synchysis) in order for typical, nonpathologic posterior vitreous detachment to take place. An incomplete or irregular progression of these events will lead to abnormal vitreomacular adhesions (VMA). This abnormal severance of the vitreous from the retina was given the descriptive term “anomalous PVD” by Jerry Sebag, MD, in 2004 to depict the disconnect between vitreous liquefaction and deterioration of vitreoretinal adherence.²

Given the aging of the population and longer life expectancy, the incidence of AMD, and specifically neovascular AMD, is steadily increasing. Neovascular AMD now affects over 1.2 million people in the United States alone. Although the precise mechanism whereby vitreomacular traction contributes to the development of neovascular AMD, or whether in fact it actually has a definite causative role, is incompletely understood, accumulating evidence suggests that there may be a relationship. For example, it is estimated that approximately one-third of eyes with neovascular AMD have VMA.^{6,7} The need for effective diagnosis and management of these patients is expected to rise as prevalence figures grow. Vitreomacular traction leading to idiopathic macular hole affects 3.3 people per 1,000 patients older than 55.⁸ Macular holes close spontaneously in only approximately 3% to 11% of cases, while some 75% of stage 2 macular holes progress to stage 3 or 4, which can only be treated with a surgical intervention.⁹

Vitreous adhesions generate tangential tractional forces on the retina, and the degree of traction exerted, in combination with the location of the adhesion, can produce varied outcomes. The vitreous in some disease states, such as diabetes and AMD, has unique structural and biochemical qualities that can also produce varied structural and functional outcomes. As a result of these distinctive characteristics, a partially detached vitreous in these patients can lead to poorer prognosis and must be carefully considered.

It has been determined that incomplete vitreous detachment and resulting vitreomacular adhesion may contribute to the pathogenesis of vitreomacular traction syndrome, macular holes, macular edema, proliferative retinopathies and exudative AMD, making VMA the initiator to numerous serious ocular events.^{3,4} The resulting VMA-related disorders must be managed efficiently, as rapid visual deterioration and poor visual function may occur.⁵

As advancements in imaging and diagnostics have been made, the role of the vitreous in many ocular conditions is becoming better understood. High-resolution optical coherence tomography provides physicians with tremendous detail of the vitreoretinal interface and can verify the presence of VMA before symptoms of metamorphopsia or visual acuity deterioration are detectable. Longitudinal OCT images provide the capacity to view subtle changes in the retina over time, allowing for careful observation of these patients. These visualization capabilities allow for “watchful waiting” of patients with disorders related to symptomatic VMA (sVMA). This remains the most common and currently accepted method of management.

TREATMENT

When eyes with sVMA produce notable visual symptoms in patients (visual deterioration or metamorphopsia), timely intervention is required to slow or halt progression and restore vision and ocular structure. Symptoms are often balanced against the risks involved with surgical intervention.

Vitrectomy is the accepted method of relieving the adhesion and the resulting tractional forces. However, dissecting the posterior hyaloid from the macular surface can be particularly difficult due to the transparency of the vitreous. In addition, mechanical separation has been shown to leave vitreous fibrils on the ILM, which can further lead to cellular proliferation, forming a scaffold to generate further traction.^{9,11}

Surgery is also associated with notable complications, and some cases may result in prolonged face-down time. Although significant advances in surgical instrumentation and techniques have taken place, the vitrectomy procedure remains challenging and requires skill and experience. There are instances in which pars plana vitrectomy may not be ideal, as it has been proposed that the surgical procedure may shorten the half-lives of intravitreal treatments.¹⁰

Over the past decade, pharmacologic options to treat sVMA have also been considered to assist physicians in treating patients in earlier stages of disease development or to be used as supplements to surgical procedures. Pharmacologic options provide an opportunity to offer patients the reduced risks of an office-based treatment or enhancement to surgery. Research developments to relieve sVMA pharmacologically have produced wide-ranging results with varied products over the past 10 years. Investigation into the benefit of intervention prior to the presence of serious symptoms is also being studied. Offering earlier relief of retinal adhesion provides a viable alternative to watchful waiting as a preventable treatment option.

The first pharmacologic options, proposed to supplement vitrectomy, used enzymatic agents. Their action was referred to as "enzymatic vitreolysis."^{12,13} In 1998, the term "pharmacologic vitreolysis" was introduced to differentiate between enzymatic and nonenzymatic methods.² More recently, in 2009, a reclassification was proposed, in order to better describe the biologic action taking place. This reclassification includes liquefactants and interfactants.¹⁴

Hyaluronidase liquefactants were initially introduced to cleave hyaluronan and the collagen complex, producing liquefaction of the vitreous; however, the initial studies in rabbit models failed to induce the desired result of PVD.¹⁵ Chondroitinase was studied as an adjunct to vitrectomy in primate and human donor eyes, although its original application was to detach epiretinal membranes. It did accomplish PVD without damage to the ILM,¹⁶ although further research on porcine eyes yielded conflicting results regarding the induction of PVD.^{17,18} To date, no further studies on human eyes have been published.

Collagenase, a bacterial agent, was investigated for use as an adjunct to vitrectomy to remove epiretinal membranes. Studies indicated that destructive hemorrhages resulted from the digestive action of bacteria on retinal vessels.¹⁹ Vitrase, a highly purified hyaluronidase, was studied in a clinical trial of 1,125 patients with persistent vitreous hemorrhage with an endpoint of hemorrhage clearance, rather than induction of PVD.²⁰ Vitrase did achieve hemorrhage clearance in more than 30% of studied eyes and successfully liquefied the vitreous gel, but separation of the vitreous cortex and ILM was not accomplished.

Dispase had the ability to cleave type 4 collagen, a key structural protein in ILM and fibronectin, which induces PVD in porcine and cadaver eyes.^{21,22} Although a vitreoretinal dehiscence was created, liquefaction was not achieved.

Plasmin is a nonspecific serine protease, which provides action on glycoproteins and activates endogenous metalloproteinases.⁴ It has been reported to facilitate PVD when used as an adjunct to surgery in human eyes, resulting in a cleaner ILM surface.¹¹ To formulate plasmin, plasminogen must be converted in vitro by streptokinase prior to surgery. This makes plasmin highly unstable and not easily accessible. Tissue plasminogen activator was predicted to supply the solution to

the challenges of autologous plasmin; however, early studies conducted on human eyes reported retinal toxicity.²⁴

Considering all of the previous findings of potential pharmacologic options for the treatment of sVMA, it can be concluded that the ideal solution must be stable and easily available, induce appropriate liquefaction and dehiscence, resolve sVMA and produce a clean PVD, with no damage or toxicity to the retina.

Ocriplasmin (ThromboGenics) is a recombinant truncated form of human plasmin (microplasmin), and contains only the catalytic domain of human plasmin, sharing all its catalytic properties. Ocriplasmin has efficacious proteolytic activity against major components of the vitreoretinal interface and produces induction of both liquefaction in the vitreous and vitreous detachment at the ILM.

Proof-of-concept studies were conducted with the primary objective of determining the vitreolytic effect, efficacy of PVD induction, and safety of intravitreal injections of ocriplasmin in the eyes of mice and post-mortem humans.¹¹ The results concluded that ocriplasmin was well tolerated and effectively induced PVD by vitreous liquefaction and vitreoretinal separation.

In 2004, a phase 2a trial (MIVI-I) investigated a dose escalation of intravitreal ocriplasmin for patients undergoing surgical vitrectomy for vitreomacular traction maculopathy or macular hole formation.²⁵ Following its successful completion, a phase 2b, sham-injection-controlled, dose-ascending trial (MIVI-IIT), was launched, evaluating 60 patients from three European clinical sites, for the safety and efficacy of ocriplasmin for the treatment of vitreomacular traction, including macular holes.

Ocriplasmin has been well tolerated, and over one-third of patients had resolution of vitreomacular traction, including macular hole closure in three of the eight macular hole cases, within 28 days, eliminating the need for vitrectomy.²⁶

Most recently, MIVI-III—a phase 2b, multicenter, randomized, placebo-controlled, double-masked, doseranging clinical trial—evaluated three doses of ocriplasmin (25, 75 and 125 µg) vs placebo in 125 patients scheduled for vitrectomy, at 19 sites in the United States.²⁷ This trial assessed the safety and efficacy of an ocriplasmin intravitreal injection seven days prior to scheduled vitrectomy. Results indicated that ocriplasmin was well tolerated and showed a defined dose-response curve. Over 30% of study patients had resolution of their underlying disease.²⁷

These results prompted the development of two additional large phase 3, international, multicenter, randomized, placebo-controlled, double-masked trials (the MIVITRUST trials) to evaluate 125 µg ocriplasmin vs placebo (0.1 mL), administered via an intravitreal injection, for the treatment of patients with sVMA. The results of the MIVITRUST clinical program demonstrated that ocriplasmin, when compared to placebo, met all primary and secondary endpoints with high statistical and clinical significance.

CONCLUSIONS

Anomalous PVD resulting in symptomatic vitreomacular adhesion has been implicated in the pathogenesis of vitreomacular traction syndrome, macular holes, DME, diabetic retinopathy and exudative AMD.^{3,4} Eyes with VMA-related disorders can experience rapid deterioration of vision and function if not managed in a timely and effective manner.⁵ The prevalence of many of these serious disorders is rising, and effective care and management of these specialized patients is currently limited to vitrectomy; however, vitrectomy is accompanied by potential complications and is not an ideal option for a number of patients with this diagnosis.

The current strategy of observation and watchful waiting until symptoms worsen should be re-evaluated, particularly if a viable and safe treatment option is available. Early intervention in cases of symptomatic VMA may be advantageous in limiting the deterioration of visual acuity, visual function and ocular structure. Pharmacologic options for the treatment of anomalous PVD and associated sVMA have advanced over the past decade. In particular, the clinical development of ocriplasmin as a pharmacologic option for the treatment of sVMA has produced promising results. It has been well tolerated and proved effective in a large phase 3 trial, at the defined optimal dose of 125 µg.

A safe and efficacious pharmacologic option to manage symptomatic VMA patients would fulfill a need to provide a safer and more effective treatment for a growing subset of patients. Intervening early, relieving vitreoretinal adhesion and related sequelae, and avoiding the complications of surgery and prolonged monitoring may present a promising possibility and opportunity to physicians and patients. **RP**

REFERENCES

1. Ponsioen TL, van Luyn MJ, van der Worp RJ, van Meurs JC, Hooymans JM, Los LI. Collagen distribution in the human vitreoretinal interface. *Invest Ophthalmol Vis Sci.* 2008;9:4089-4095.
2. Sebag J. Anomalous posterior vitreous detachment: a unifying concept in vitreo-retinal disease. *Graefes Arch Clin Exp Ophthalmol.* 2004;242:690-698.
3. Sebag J. Pharmacologic vitreolysis. *Retina.* 1998;18:1-3.
4. Gandorfer A, Kampik A. Pharmacologic vitreolysis combining the two enzymes plasmin and hyaluronidase. *Retina.* 2009;29:1097-1105.
5. Koerner F, Garweg J. Vitrectomy for macular pucker and vitreomacular traction syndrome. *Doc Ophthalmol.* 1997;97:449-458.
6. Krebs I, Brannath W, Glittenberg C, Zeiler F, Sebag J, Binder S. Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration? *Am J Ophthalmol.* 2007;144:741-746.
7. Robison CD, Krebs I, Binder S, et al. Vitreomacular adhesion in active and endstage age-related macular degeneration. *Am J Ophthalmol.* 2009;148:79-82.e2.
8. Moshfeghi A, Salam GA, Deramo VA, et al. Management of macular holes that develop after

- retinal detachment repair. *Am J Ophthalmol.* 2003;136:895-899.
9. Gandorfer A. Ocriplasmin-assisted vitrectomy. *Dev Ophthalmol.* 2009; 44:26-30.
 10. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB 3rd, Miller M. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. *Ophthalmology.* 2003;110:681-686.
 11. Gandorfer A, Ulbig M, Kampik A. Plasmin-assisted vitrectomy eliminates cortical vitreous remnants. *Eye.* 2002;16:95-97.
 12. Ramesh S, Bonshek RE, Bishop PN. Immunolocalisation of opticin in the human eye. *Br J Ophthalmol.* 2004;88:697-702.
 13. Hindson VJ, Gallagher JT, Halfter W, Bishop PN. Opticin binds to heparan and chondroitin sulfate proteoglycans. *Invest Ophthalmol Vis Sci.* 2005;46:4417-4423.
 14. Sebag J. Pharmacologic vitreolysis—premise and promise of the first decade. *Retina.* 2009;29:871-874.
 15. Hikichi T, Kado M, Yoshida A. Intravitreal injection of hyaluronidase cannot induce posterior vitreous detachment in the rabbit. *Retina.* 2000;20:195-198.
 16. Hageman GS, Russell SR. Chondroitinase-mediated disinsertion of the primate vitreous body. *Invest Ophthalmol Vis Sci.* 1994;35:1260.
 17. Hermel M, Schrage NF. Efficacy of plasmin enzymes and chondroitinase ABC in creating posterior vitreous separation in the pig: a masked, placebo-controlled in vivo study. *Graefes Arch Clin Exp Ophthalmol.* 2007;245:399-406.
 18. Staubach F, Nober V, Janknecht P. Enzyme-assisted vitrectomy in enucleated pig eyes: a comparison of hyaluronidase, chondroitinase, and plasmin. *Curr Eye Res.* 2004;29:261-268.
 19. Takahashi K, Nakagawa M, Ninomiya H, et al. Enzyme-assisted vitrectomy with collagenase. *Jpn J Clin Ophthalmol.* 1993;47:802-803.
 20. Kuppermann BD, Thomas EL, de Smet MD, Grillone LR; Vitrase for Vitreous Hemorrhage Study Groups. Safety results of two phase III trials of an intravitreal injection of highly purified ovine hyaluronidase (Vitrax) for the management of vitreous hemorrhage. *Am J Ophthalmol.* 2005;140:585-597.
 21. Tezel TH, Del Priore LV, Kaplan HJ. Posterior vitreous detachment with dispase. *Retina.* 1998;18:7-15.
 22. Oliveira LB, Tatebayashi M, Mahmoud TH, Blackmon SM, Wong F, McCuen BW 2nd. Dispase facilitates posterior vitreous detachment during vitrectomy in young pigs. *Retina.* 2001;21:324-331.
 23. Wang F, Wang Z, Sun X, Wang F, Xu X, Zhang X. Safety and efficacy of dispase and plasmin in pharmacologic vitreolysis. *Invest Ophthalmol Vis Sci.* 2004;45:3286-3290.
 24. Chen SN, Yang TC, Ho CL, Kuo YH, Yip Y, Chao AN. Retinal toxicity of intravitreal tissue plasminogen activator: case report and literature review. *Ophthalmology.* 2003;110:704-708.
 25. de Smet MD, Gandorfer A, Stalmans P, et al. Ocriplasmin intravitreal administration in patients with vitreomacular traction scheduled for vitrectomy: the MIVI I trial. *Ophthalmology.* 2009;116:1349-1355.
 26. Stalmans P, Delaey C, de Smet MD, van Dijkman E, Pakola S. Intravitreal injection of

ocriplasmin for treatment of vitreomacular adhesion: results of a prospective, randomized, sham-controlled phase II trial (the MIVI-IIT trial). *Retina*.2010;30:1122-1127.

27. Benz MS, Packo KH, Gonzalez V, et al. A placebo-controlled trial of microplasmin intravitreal injection to facilitate posterior vitreous detachment before vitrectomy. *Ophthalmology*. 2010;117:791-797.

Peter Stalmans, MD, PhD, is associate professor of ophthalmology at UZ Leuven in Belgium. He reports minimal financial interest in Thrombogenics. Dr. Stalmans can be reached at peter.stalmans@uzleuven.be.