

A New Focus on the Vitreous and Its Role in Retinal Function

BY PRAVIN U. DUGEL, MD

Since Robert Machemer, MD, performed his first vitrectomy, the field of vitreoretinal surgery has been the beneficiary of tremendous advances in technology. The pace of improved imaging modalities, enhanced surgical techniques coupled with smaller instrumentation, and paradigm-changing pharmacotherapeutics has been dramatic. Ironically, despite all these advances, many of us considered the vitreous as little more than the gelatinous space that stands between the anterior segment and the retina. New data, however, have revealed that the vitreous plays a bigger role in overall retinal function than previously thought. A PubMed search of the term “vitreous” demonstrates the exponential increase in our understanding of this seemingly plain structure in the past 2 decades. These advances continue to help shape our understanding of the impact of the vitreous in the development and progression of retinal disease.

With the aging of the population, an increasing number of patients are being identified with complications arising from an aging vitreous. Posterior vitreous detachment (PVD) is a natural occurrence with aging, in which the vitreous degenerates, a process called liquefaction, and releases itself from the vitreoretinal interface, a process called syneresis.^{1,2} In an ideal situation, these 2 steps occur naturally and in synchrony. In some cases, however, anomalous (incomplete) PVD occurs, resulting in vitreomacular adhesion (VMA). Vitreomacular traction (VMT) occurs when the vitreous pulls away at the areas of adhesion.^{3,4} Ultimately the

consequences of incomplete PVD and retinal traction vary depending on where and how firmly the posterior vitreous is attached.

THE IMPLICATIONS OF PVD

Almost 10 years ago, J Sebag, MD, described the implications of anomalous PVD.⁵ The vitreous can split to form a schisis and a partial thickness PVD, resulting in traction. If the traction goes outward, a macular hole may result. If the traction goes inward, an epiretinal membrane (ERM) or macular pucker may form. A full-thickness separation of the vitreous may occur, but it may be trapped. If in the posterior pole, and posterior traction occurs with peripheral separation, macular traction may result. Macular traction can cause VMT syndrome, but it is also linked to many other conditions such as neovascular age-related macular degeneration, diabetic retinopathy, diabetic macular edema, and retinal vein occlusion.⁶⁻¹¹ If traction occurs at the optic disc, vitreopapillary syndrome, and ensuing disc edema, can occur, and if there is posterior separation but peripheral traction, retinal tears and retinal detachment can occur.

It is interesting to see how VMA resulting from anomalous PVD is involved in so many diseases. I think that we are gaining more understanding because our imaging techniques are now married with what we know about the pathophysiology of this process.

There is compelling evidence to suggest that PVD may be protective against AMD, whereas VMA may promote

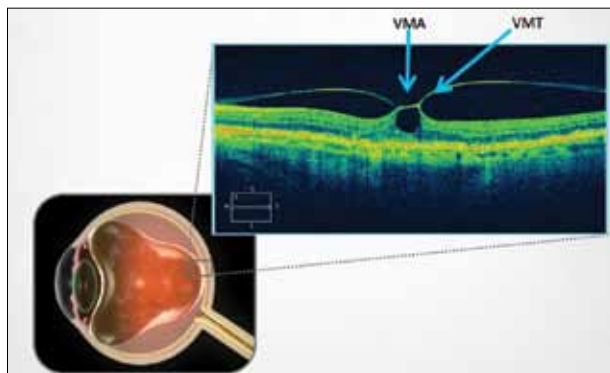


Figure 1. If left untreated, VMA can progress to VMT and macular hole.

exudative AMD.¹² There is also evidence demonstrating that persistent PVD may be a risk factor for exudative AMD due to inflammation-induced vitreoretinal traction.¹³

Recent data have also linked VMA with diabetic retinopathy. There are data showing that approximately one-quarter of patients with diabetic macular edema (DME) have identifiable VMA.¹¹

The use of spectral-domain optical coherence tomography (OCT) has led to a realization that the prevalence of VMA has been underestimated.¹⁴ Our improved ability to visualize the vitreoretinal interface and detect VMA allows early diagnosis and treatment of this condition, which if left untreated can progress to VMT and macular hole (Figure 1). As OCT technology continues to improve, progress on understanding the role of VMA in retinal disorders is likely to grow considerably as well. This point has been substantiated by the new designation of an ICD-9 diagnostic code for VMA, 379.27.

OPTIONS FOR SYMPTOMATIC VMA

The effects of symptomatic VMA include metamorphopsia, deteriorating visual acuity, and, in some cases, a severe loss of vision (Figure 2). Current options to treat VMA are watchful waiting and vitrectomy.

A study of the natural history of VMA showed that most patients (81%) with VMA experienced cystoid changes.¹⁵ Of those patients, 67% had cystoid macular changes that persisted through a follow-up period of 60 months and lost a mean 2 lines of vision, with some patients losing more than 6 lines of vision. Spontaneous complete PVD occurred in only 11% of patients.

Vitrectomy to induce PVD and release traction on the retina is used for treating symptomatic VMA. The standard pars plana vitrectomy (PPV) 3-port 20-gauge vitrectomy has now been largely supplanted by microincisional vitrectomy (23 or 25 gauge), reducing postoperative discomfort and promoting faster visual rehabilitation.¹⁶ Although microincisional vitrectomy is thought by some surgeons to be safer, it is not without complications. The complications that can occur with vitrectomy include a potentially higher incidence of intraoperative or postoperative retinal breaks,¹⁷ retinal detachment,¹⁸⁻²⁶ and endophthalmitis.²⁻¹⁰ Other potential complications include possible incomplete separation of the vitreous and epiretinal membrane (ERM); development of fibrovascular membranes; and iatrogenic trauma to the retina.

Another potential treatment option is pharmacologic vitreolysis, the intravitreal use of enzymatic agents to promote vitreous separation from the retina.

The primary goals of pharmacologic vitreolysis are to cleave the vitreoretinal interface and alter the molecular organization and structure of the vitreous to reduce or eliminate its role in disease formation.²⁷ The potential

benefits of pharmacologic vitreolysis include complete atraumatic posterior vitreous separation; an intact physiologic vitreoretinal interface; prevention of fibrovascular proliferation; and treatment of retinal edema and exudation.^{28,29}

Several agents have been explored; however, ocriplasmin (formerly known as microp lasmin; Figure 3) is the agent that has shown the greatest potential. Ocriplasmin (ThromboGenics) is a truncated form of human plasmin that retains the catalytic properties of the original molecule but is more stable. Ocriplasmin is engineered via recombinant DNA

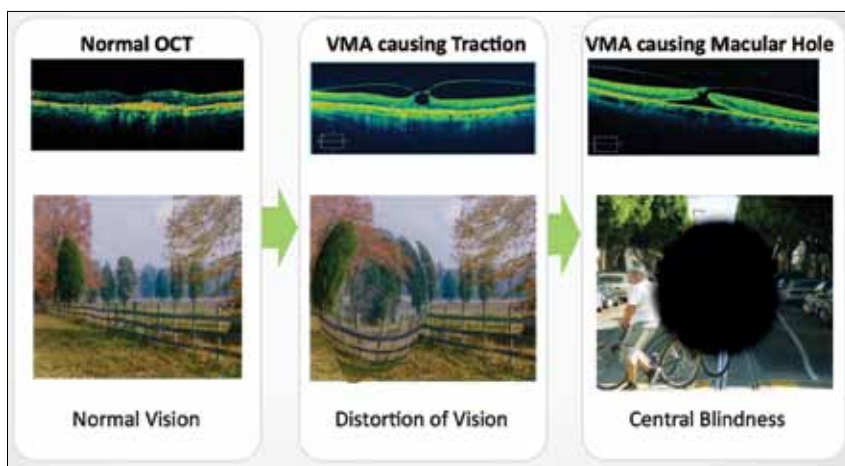


Figure 2. The effects of symptomatic VMA include metamorphopsia, deteriorating visual acuity, and, in some cases, a severe loss of vision.

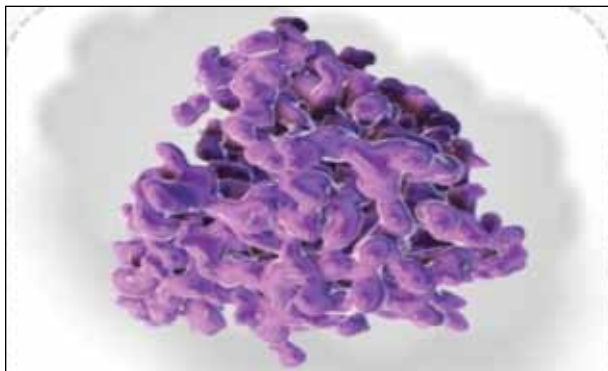


Figure 3. Ocriplasmin is a truncated form of human plasmin that retains the catalytic properties of the original molecule but is more stable.

technology and induces resolution of VMA via a 2-step mechanism that includes vitreous liquefaction and vitreoretinal separation (Figure 4).³⁰ It has been studied for nearly a decade, and approximately 1000 patients have been treated in the combined clinical program (phase 1, 2 and 3 clinical trials).

In 2 large phase 3 studies designed to assess the safety

and efficacy of ocriplasmin to induce pharmacologic resolution of VMA, a single intravitreal dose of 125 μ g ocriplasmin achieved statistical and clinically significant results in eyes with VMT and full-thickness macular hole.³⁰ A single injection of ocriplasmin achieved a pharmacologic VMA resolution rate of almost 30% in patients with VMT and a pharmacologic full-thickness macular hole closure rate of 40%. The resolution of these anatomic abnormalities resulted in clinically significant improvements in visual acuity. Most adverse events were transient and temporary and were mostly noted between day 0 and day 7. If approved by the US Food and Drug Administration, ocriplasmin will have a prodigious impact on a broad spectrum of vitreoretinal diseases.

SUMMARY

Increasing awareness of the vitreous and its role in the pathology of retinal disease is important in advancing the management of vitreoretinal disorders, such as VMA. Advancements in imaging capabilities and new therapies will aid vitreoretinal specialists in diagnosing and treating sight-threatening diseases earlier than we would have in the past. We are on the precipice of not only better

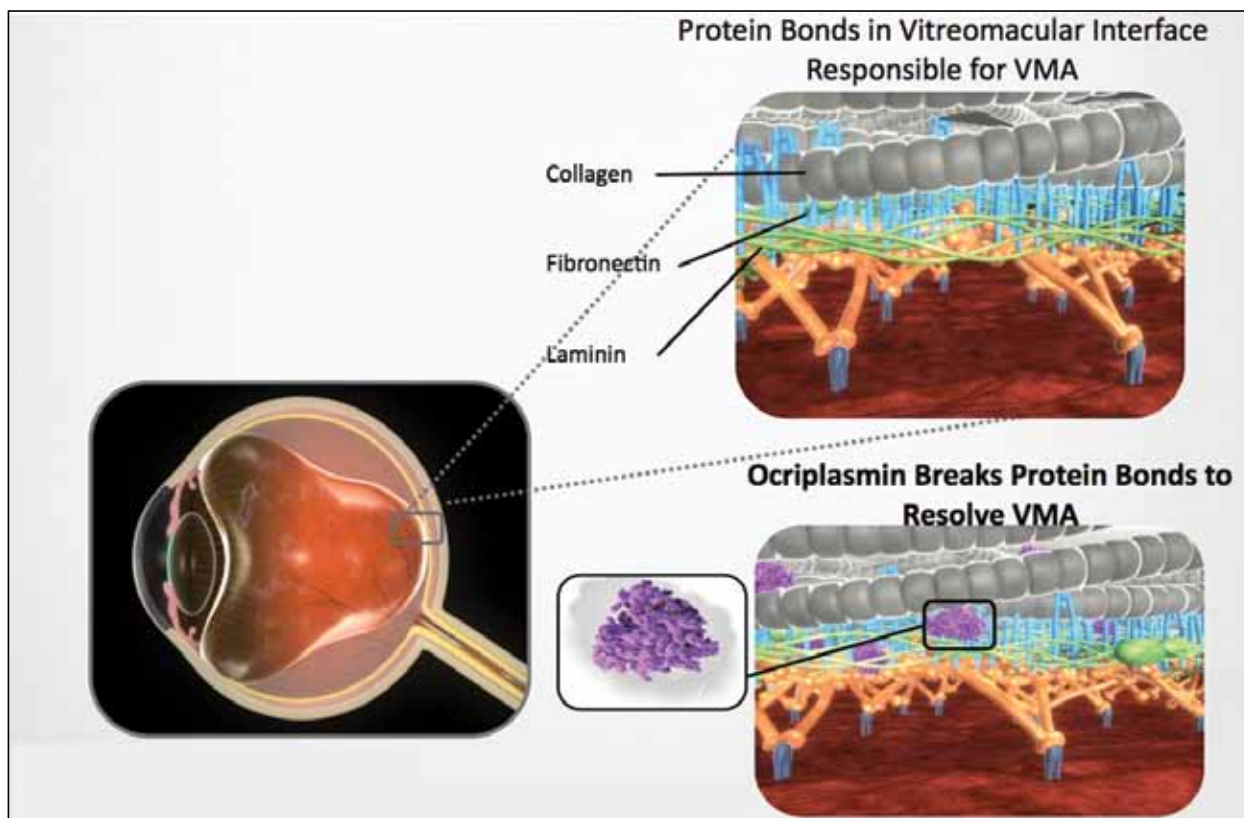


Figure 4. Ocriplasmin is engineered via recombinant DNA technology and induces resolution of VMA via a 2-step mechanism that includes vitreous liquefaction and vitreoretinal separation.

understanding the role of the vitreous in various retinal diseases, but most important, of treating the vitreous pathology. The potential impact of pharmacologic vitreolysis for our patients is profound. A new chapter in patient treatment is about to begin. ■

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