Posterior vitreous detachment (PVD), in the great majority of people, is a relatively benign process that occurs with aging. The vitreous gel, solid in infancy and youth, liquefies over time, and the adhesion between the vitreous and the retina concurrently weakens. When sufficient liquefaction and weakening of adhesion at the vitreoretinal interface have taken place, usually between the ages of 40 and 60 years, the vitreous collapses and pulls away from the retina. At this point, patients may see floaters, and in the preponderance of cases that is the end of the story of PVD.

In some patients, however, gel liquefaction exceeds the pace of vitreoretinal dehiscence, resulting in anomalous PVD. With the vitreous only partially detached, traction on the retina can lead to a number of clinical manifestations depending on where vitreoretinal adhesion is strongest. When the anomalous PVD is in the periphery, retinal tears and detachments can result. When there is vitreomacular adhesion (VMA), it can result in vitreomacular traction (VMT) syndrome, macular hole or macular pucker. In addition, anomalous PVD appears to have deleterious effects in exudative age-related macular degeneration (AMD) and diabetic macular edema (DME).

Management of the sequelae of anomalous PVD and VMA has historically been surgical, even in AMD and DME, but the era of pharmacologic vitreolysis is arriving. PVD and VMA and examines the changing landscape of management for these conditions.

VITREOMACULAR ADHESION

Vitreomacular traction is a term that has been used to describe one manifestation of anomalous PVD. There are problems with the term, however, because traction is a force, and we cannot measure that in the eye. We can only observe vitreomacular adhesion (VMA), through physical examination and imaging and infer traction. In recognition of this distinction, a new disease code for this entity was added to the ICD-9-CM listing last October, designated “VMA.”

VMA, and what we assume to be traction, result from anomalous PVD, a phenomenon that I described several years ago as a useful unifying concept in vitreoretinal disease. The concept of anomalous PVD offers a way to better understand various diseases that were previously thought to be quite different from one another, when in fact they are just different manifestations of the same fundamental pathophysiology.
The apparent traction on the retina caused by anomalous PVD leads to different types of pathology depending on where vitreoretinal adhesion persists and the vector of traction. If traction is axial and occurs in the peripheral retina, retinal tears or detachment can result. If axial traction occurs in the macula, VMT syndrome or exacerbation of AMD or DME can occur. When traction is axial and occurs in the macula, and if vitreous is still adherent to the optic disc, the vector of forces is outward from the fovea (centrifugal tangential traction), causing macular hole. If there is no adhesion of vitreous to the optic disc, the forces of tangential traction are inward, toward the center of the fovea (centripetal tangential traction), which can ripple the underlying retina into folds resulting in macular pucker. These pathophysiologies, once thought to be separate entities, are all manifestations of anomalous PVD.

The subset of patients with anomalous PVD who have VMA are among the most symptomatic because the macula is the area of detailed central vision. Symptoms vary with the subtypes of vitreomacularopathy but generally include distortions, blurred vision, and central visual field defects.

**TREATMENT: SURGICAL**

Thanks to advances in imaging technologies, we have much greater diagnostic acumen for these vitreomacularopathies than ever before, and we are able to tailor our therapeutic approach to the specific subtypes that affect a particular patient. In the case of macular pucker, macular hole, and severe VMT syndrome, when vision is sufficiently affected and the patient is unhappy, surgical intervention is the standard of care.

The objective of surgery for VMA is to relieve traction by lysing the adhesion between vitreous and macula. Fortunately, in the overwhelming majority of cases, this is straightforward. In surgery we perform vitrectomy to gain access to the site of VMA and then peel off the vitreous attachment from the macula. The concern is that in so doing one may tear off a piece of the retina, but fortunately that does not usually occur. For example, Figure 1 shows an extreme manifestation of VMT syndrome. In this eye the entire retina in the macular region appears to have been pulled forward by axial traction. This female patient had profound loss of central vision, with a visual acuity of 20/400. During surgery, I was very concerned that I was going to unroof that dome of tissue and leave her with a hole and poor vision. Fortunately that did not happen, and I was able to peel off the adhesions without incident. Her final visual acuity was 20/40.

The challenge of peeling the membrane off the retina has been improved, in certain macular hole cases, with chromodissection, an approach that involves the use of dyes to stain the membrane and facilitate its removal. The use of dyes is typically not necessary for macular pucker or VMT syndrome surgery.

Recent improvements in surgical equipment have significantly changed the approach to surgery for these conditions. I now perform 95% of surgeries using sutureless techniques with 25-gauge instruments under local anesthesia in an ambulatory surgery center. Surgery that used to take over an hour now takes 20 to 30 minutes. The reduction in surgical time and invasiveness results in faster rehabilitation, as patients now recover in a few weeks.

**TREATMENT: PHARMACOLOGIC**

Although there have been significant improvements in our surgical approaches to VMA and its varied manifestations, it is nonetheless invasive surgery—costly, labor-intensive, fraught with hazards, and with an extended period of healing for the patient. It would thus be desirable to obviate the need for surgery. Fortunately, we appear to be entering an era when this, and more, may be possible.

Pharmacologic vitreolysis is a term I coined in 1998 to refer to the biochemical manipulation produced by certain drugs to the macromolecular structure of the vitreous, and to the vitreoretinal interface, to produce innocuous PVD: ie, complete separation of the vitreous from the retina without damage to the retina.
Pharmacologic agents to facilitate vitreoretinal surgery were first sought in pediatric patients, where the adherence of the vitreous to the retina is the firmest. In the ensuing years, a variety of pharmacologic agents have been investigated in the quest to produce innocuous PVD, including plasmin, tissue plasminogen activator, chondroitinase, hyaluronidase, and others. When I introduced the concept of pharmacologic vitreolysis, I surveyed the field and grouped these agents in terms of their biochemical properties, as enzymatic and nonenzymatic, and within the enzymatic group as nonspecific and substrate-specific agents. In the past decade my thinking has evolved; it seems that the chemical nature of these agents is less interesting than their biologic properties. Therefore, I recently reorganized the agents in 2 categories: those that liquefy the vitreous, called liquefactants, and those that produce vitreoretinal dehiscence or weakening of the vitreoretinal interface, called interfactants. Within each of those categories are nonspecific and substrate-specific agents, most of which are enzymatic but some nonenzymatic.

This seems a more useful way to approach the objectives, which are to liquefy the gel vitreous and weaken vitreoretinal adhesion. For these purposes we want agents that are both liquefactants and interfactants, and if a given agent does not have both of these qualities to a sufficient degree, combinations of agents may be needed. In the pharmacologic vitreolysis cocktail, where more than 1 agent is combined, the relative concentrations of the agents would vary depending on the disease being treated, the age of the individual, the severity of the disease, the chronicity of the disease, and so on. It remains to be determined which agents in which combinations will achieve the ideal results in a given patient with a given pathophysiology.

One vitreolytic agent that has received attention recently is microplasmin, also known as ocriplasmin (ThromboGenics), a recombinant form of a truncated plasmin molecule. This agent is both a liquefactant and interfactant. It is a nonspecific protease; that is, it digests all proteins. Therefore, there is a theoretical risk there could be untoward side effects if the action of ocriplasmin is not specific to the proteins we want to target in a particular disease. At this time, however, we do not really know which proteins we want to target, so use of a nonspecific approach is not unreasonable. I was an investigator in the phase 2 and phase 3 trials for the use of microplasmin to relieve VMA, and there did not appear to be any untoward side effects.

Those studies showed statistically significant efficacy in the ability of ocriplasmin to relieve VMA in patients who are symptomatic; 26.5% of patients achieved the primary endpoint of pharmacologic VMA resolution at day 28 after 1 injection of ocriplasmin, and, of those patients, approximately 75% experienced resolution within 1 week of injection. In patients with macular holes, more than 40% achieved closure after 1 injection, and this increased to 60% for holes smaller than 250 µm.

**AMD AND DME**

The greatest impact of pharmacologic vitreolysis may not be in the treatment of primary vitreomacular pathologies, but rather in treating far more common posterior segment pathologies, such as AMD and DME, where VMA is a contributing factor that aggravates the primary pathology, worsening the prognosis and adversely impacting vision. These diseases both have major impacts on vision, not only in terms of the profound nature of the vision loss they cause, but also because of their high prevalences. There are many more people with either DME or AMD than with all of the vitreomacular pathologies combined. Diabetic retinopathy is the leading cause of blindness in Americans between the ages of 20 and 74, and the overwhelming majority of this vision loss is due to DME. AMD is the leading cause of blindness in the elderly, and with the aging population this problem will only get bigger. There is the potential, therefore, that pharmacologic vitreolysis may have a major impact on these serious and common blinding diseases. In contrast to the aforementioned vitreomacular pathologies, where the primary disease is the result of VMA, in DME and AMD the underlying disease can be worsened by the presence of VMA, and by extrapolation if we can relieve the VMA there may be a salubrious effect on the underlying diseases.

Studies have shown, in the case of diabetic retinopathy, that the severity of the disease is much greater when the vitreous is attached to the retina than when it is detached. Similarly, in AMD, studies have demonstrated that an individual who has AMD is less likely to develop CNV and exudation with the vitreous detached rather than attached.
Although it is possible that surgery to relieve VMA would have a positive effect in DME and AMD, there has been understandable reluctance within the retina community to propose widespread surgical intervention for these patients. The exception has been in individuals with DME who have been unresponsive to laser therapy and anti-VEGF therapy. In those individuals, vitrectomy with membrane peeling improves the structure and function of the macula. This evidence suggests that release of VMA has beneficial effects in DME. Thus, rather than subjecting DME patients who are not responding to laser and anti-VEGF therapy to surgery, perhaps pharmacologic vitreolysis should be performed first. A trial to investigate the safety and efficacy of this approach would be worthwhile, as might a similar trial in patients with wet AMD. We may even find that the relief of VMA with pharmacologic vitreolysis improves the response to anti-VEGF injections and stabilizes wet AMD.

CONCLUSIONS

To date, treatments for symptomatic VMA have all been surgical, but we are now entering the age of pharmacologic treatment. A good percentage of macular holes can now be closed with an injection in the office, as opposed to surgery. That is terrific news, and I have hopes we will be able to improve these numbers with a variety of approaches now being investigated: different delivery systems, different dosing regimens, multiple injections, and combination with other pharmacologic vitreolysis agents, to name a few.

The use of pharmacologic vitreolysis agents as adjuncts to surgery represents a first phase in the introduction of pharmacologic therapy for VMA. We are now entering a second phase, where the need for disease treatment is obviated with pharmacologic intervention. The Holy Grail for pharmacologic vitreolysis is the development of agents that can induce an innocuous PVD before disease even occurs. That is to say, some time in the future we may understand these diseases so well that we will be able to predict which individuals will develop the various vitreomacularpathies, severe DME, or wet AMD, and we will induce innocuous PVD in those individuals before the disease manifests. This will fulfill the promise of modern medicine, which is to understand diseases sufficiently so that we not only can replace surgical therapy with noninvasive pharmacologic treatments, but can prevent the disease from happening at all. That is the natural evolution of medicine, and I believe pharmacologic vitreolysis is the perfect paradigm for that evolution. I find it extremely exciting to see this development progressing over a relatively short period of time.

As exciting as it is to see the potential for pharmacologic vitreolysis developing, there are 2 additional factors to consider. First, these therapies do no good if we do not get them to our patients. We must raise awareness among general ophthalmologists, optometrists, family practitioners, and patients themselves, that we have new ways to treat the vitreomacularpathies. Second, we must think about how to identify high-risk individuals and intervene early in the natural histories of these diseases so as to prevent, and not just correct, vision loss.

Above all, we must not become complacent. Just because 1 agent for pharmacologic vitreolysis has demonstrated statistical significance does not mean it has achieved its greatest possible clinical significance. We must strive to develop greater clinical significance for these therapies in the coming years.

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