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The Charles Schepens Lecture: Management Options for Vitreomacular Traction:

Use an Individualized Approach

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Abstract

Purpose—To present the management options for vitreomacular traction (VMT) and to recommend an individualized approach to treatment selection.

Design—Presented at the American Academy of Ophthalmology Annual Meeting, 2016, Chicago, October 15, 2016 (The Charles Schepens Lecture).

Participants—None.

Methods—Review of published literature and clinical trials.

Main Outcome Measures—Visual and anatomic outcomes of various treatment options for VMT were reviewed.

Results—The management options for VMT include pars plana vitrectomy, pneumatic vitreolysis, enzymatic vitreolysis, and observation. The surgical management using pars plana vitrectomy offers the most effective approach for VMT, but there are inherent risks and cost issues. Pneumatic vitreolysis is reported to be cost-effective and may be an anatomically successful nonsurgical option for management. Enzymatic vitreolysis with intravitreal ocriplasmin is another nonsurgical option, but both short- and long-term side effects may occur. Observation in selected patients can be associated with stable visual outcomes during long-term follow-up.

Conclusions—The final management decision should be individualized for specific patients depending on the patient's clinical findings, potential risks, probable benefits, and costs of each option.

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I am grateful to the American Academy of Ophthalmology, the Retina Research Foundation, and the Schepens International Society for their invitation to present this lecture honoring Dr Charles L. Schepens. Dr Schepens is well-known in the ophthalmic community for developing the first binocular, stereoscopic indirect ophthalmoscope (1946) and for his pioneering leadership in treating retinal detachment (Fig 1). In 1947, he started working as a research fellow at the Howe Laboratory at Harvard University. He rose through the years to become the premier retinal surgeon in the United States, and trained generations of medical students, residents, fellows, researchers, and leaders in our field. He was the editor of 4 books and authored more than 340 peer-reviewed articles. In 1999, Dr Charles Schepens was chosen by the American Society of Cataract and Refractive Surgery as one of the 10 most influential ophthalmologists of the 20th century. The American Academy of Ophthalmology named Dr Schepens as one of their Inaugural Laureates in 2003 in recognition of his many contributions in Ophthalmology.

In addition, he has been recognized for his heroics during World War II by receiving the French Legion of Honor Award for helping people escape from Nazi-occupied France into Spain. Dr Schepens is an inspiration for all of us both as a retinal surgeon and as a leader.

The normal aging process of the vitreous gel includes liquefaction of the vitreous and changes in the vitreous framework over time, leading to a final separation of the vitreous from the macula and optic nerve known as posterior vitreous detachment (PVD).¹ A PVD occurs as a result of both vitreous gel liquefaction and weakening of vitreoretinal adhesion, occurring independently but simultaneously. Although partial PVD with asymptomatic vitreomacular adhesion (VMA) can be a normal transient stage of physiologic PVD, nonphysiologic persistence of VMA may result in vitreomacular traction (VMT) with visual symptoms² (Fig 2). A VMT may cause retinal distortion, macular edema, foveal detachment, and full-thickness macular hole (FTMH), with symptoms such as photopsia and distorted or reduced vision.

In previous decades, pars plana vitrectomy (PPV) was the only treatment option for symptomatic VMT. With the development of improved diagnostic techniques and agents, nonsurgical options are also being considered. The International Vitreomacular Traction Study Group in 2013 provided a clinically applicable optical coherence tomography (OCT)–based classification system that is useful for the execution and analysis of clinical studies of disorders of the vitreomacular interface.³ In this new classification system, VMA is characterized by cortical vitreous separation from retina with vitreous gel still attached to the fovea within a radius of 3 mm of the fovea but without any change in the contour or morphology. In addition, VMT was defined as traction developing on the macula during the progression of PVD with resultant surface retinal distortion, intraretinal pseudocyst, or elevation of the fovea from the retinal pigment epithelium. A full-thickness defect in the neural layers at the fovea was classified as FTMH. It is important to consider this newer, OCT-based classification system when interpreting data from the pre-OCT literature. Some reports have used the term “symptomatic VMA,” which now corresponds with “VMT” in this newer classification system.

In the 2016 Charles Schepens Lecture, management options for patients with symptomatic VMT are presented, including both surgical and nonsurgical treatment options, which may result in equal or better visual and anatomic outcomes.

Methods

The published literature and presentations at international conferences were reviewed.

Results

Management options today for VMT include PPV, pneumatic vitreolysis, enzymatic vitreolysis, and observation. Surgical management of VMT using PPV is a traditional and widely used option with generally successful anatomic and visual outcomes. In the era before OCT, Smiddy et al⁴ (1988) reported 16 eyes that underwent PPV for VMT, and postoperative visual acuity (VA) outcomes were either stable or improved. Using diagnostic OCT, Sonmez et al⁵ (2008) reported that 21 of 24 eyes (87.5%) that underwent PPV for VMT improved by 1 line. Visual improvement was greater in the eyes with focal (or V-shaped) VMT on OCT. The visual and OCT results of PPV for symptomatic VMT were reported by Witkin et al⁶ in 2010. The mean VA in that study improved from a preoperative VA of 20/122 to a postoperative VA of 20/68 ($P = 0.005$). Improvement in vision was less in eyes with lamellar separation of the inner and outer foveal layers compared with those with only cystoid macular edema and perifoveal VMT. A meta-analysis including 21 studies (259 eyes) by Jackson et al⁷ reported a mean overall improvement from 20/93 to 20/53 in patients undergoing PPV for VMT. At least 1 line of VA improvement was reported in 64.3%, whereas improvement in VA by 2 lines was reported in 32.9% of eyes.⁷ Intraoperative and postoperative complications are possible, which may affect the anatomic and visual outcomes. Postoperative complications including retinal detachment and FTMH were reported in 4.56% and 1.44%, respectively. Gonzalez et al⁸ (2015) reported a consecutive case series of 41 patients who underwent PPV for VMT also using internal limiting membrane peeling in 93% of patients (38/41). Postvitrectomy macular hole (MH) developed in 9.8% (4/41), although no retinal detachment was noted in this cohort of patients. In a cost-effectiveness and cost utility study for the treatment options for VMA and FTMH, Chang et al⁹ (2014) reported that as a primary procedure, PPV was the most cost-effective therapy. The other treatment options had similar costs per quality-adjusted life-year saved and compared favorably with costs of therapy for other retinal diseases. In considering this surgical option, intraoperative and postoperative complications (cataract progression in phakic eyes, retinal detachment, endophthalmitis, MH formation) must be balanced with the potential benefits.

Pneumatic vitreolysis by intravitreal injection of a gas bubble destabilizes the vitreous integrity by accentuating liquefaction (synchysis) during the gas expansion phase and cortical vitreous collapse (syneresis) during the absorption phase of the bubble, leading to PVD. In a pilot study by Chan et al¹⁰ (1995) during the era before OCT, 11 patients with an impending MH (stages 1A and 1B) and 7 patients (8 eyes) with FTMH (stages 2 and 3) received gas injections. A complete PVD was achieved in 18 of 19 eyes without a prior PVD within 2 to 9 weeks after gas injection. Ten of the 11 impending holes (all 7 eyes with stage

1A MHs; 3 of 4 eyes with stage 1B MHs) resolved after gas injection. After gas tamponade, 3 of 6 early full-thickness (stage 2) MHs closed. None of the stage 3 MHs closed after gas injection. The mean best-corrected VA of the successful eyes was 20/32. There were no major complications of pneumatic vitreolysis reported in this study. In another study of pneumatic vitreolysis, Rodrigues et al¹¹ (2013) reported outcomes in 15 eyes with idiopathic VMT (n = 7), diabetic macular edema (n = 6), age-related macular degeneration (n = 1), and VMT associated with impending MH (n = 1), after a single injection of 0.3 mL of 100% C₃F₈.¹¹ The release of VMT occurred in 6 patients (40%) at 1 month and 9 patients (60%) at 6 months. The predictors of treatment success included area of adhesion <750 microns, maximum foveal thickness <500 microns, low vitreous face reflectivity, and absence of diabetic macular edema. A recent study reported outcomes of 35 eyes (34 patients) with symptomatic VMT that underwent pneumatic vitreolysis during a period of 5 years from 2010 to 2015 (Chan C, Mein C. Pneumatic vitreolysis for treatment of focal vitreomacular traction. Macula Society 2016, Miami, February 26, 2016). A complete PVD developed in 31 eyes (88.6%) at a mean (median) of 3.6 (3.5) weeks after C₃F₈ gas injection. Posterior vitreous detachment developed in 20 of 24 eyes (83.0%) with VMT only. In eyes with a small stage 2 MH, PVD with MH closure was reported in 8 of the 11 eyes (73%). Steinle et al compared the outcomes of 3 nonsurgical approaches for the management of symptomatic VMT, including intravitreal injection of SF₆ or C₃F₈ or ocriplasmin (Steinle N, Dhoot D, Pieramici DJ, et al. Comparison of three non-surgical treatments for vitreomacular traction [VMT]. ARVO 2016, Seattle, May 2, 2016. Abstract Number: 1806). The study reported outcomes of 113 consecutive patients with VMT treated with 1 of 3 interventions: 54 with intravitreal ocriplasmin, 32 with C₃F₈ gas injection, and 27 with SF₆ injections. At final follow-up, VMT release was 84% with C₃F₈, 56% with SF₆, and 48% with ocriplasmin. In their conclusions, the authors stated that C₃F₈ gas injections had superior VMT release rates compared with the other 2 methods. They also suggested that “dipping bird” movements by the patient after gas injection may assist in accelerating the vitreolysis. Although Steinle et al suggest that the dipping bird maneuver may accelerate the process of vitreous liquefaction, the value of this maneuver is questionable given that Chan and Mein had similar results without using the dipping bird maneuver.

Pharmacologic agent–assisted vitreolysis is a relatively new treatment option for the management of VMAs, including intravitreal ocriplasmin and integrin antagonist (ALG-1001 [Luminate]). Ocriplasmin–microplasmin is a 27-kDa recombinant selective serine protease subunit of human plasmin. This pharmacologic agent is capable of cleaving collagen, laminin, as well as fibronectin. In a prospective, randomized, sham-controlled phase II trial (The Microplasmin for Intravitreal Injection [MIVI-IIT] trial), Stalmans et al¹² (2010) evaluated the ability of a single or repeated injection of microplasmin to release VMT. This study enrolled 60 patients with symptomatic VMA (41, no MH; 19, stage Ib/II MHs). Within 28 days of treatment with sham or 75-, 125-, or 175-μg microplasmin, nonsurgical resolution of VMA was observed in 8%, 25%, 44%, and 27% of the patients, respectively. The results support the use of microplasmin as a nonsurgical treatment option for symptomatic VMA. Stalmans et al¹³ (2012) reported results of MIVI 006 and 007 studies, 2 multicenter, randomized, double-blind, phase III trials comparing a single intravitreal injection of ocriplasmin with intravitreal placebo. The MIVI 006 was in the

United States only and MIVI 007 was in Europe and United States. Subjects had symptomatic focal VMA, although MHs >400 microns were excluded. A total of 652 randomized patients (464 receiving ocriplasmin; 188 receiving placebo) were included in the study. The primary end point in this study was resolution of symptomatic VMA on OCT by day 28. Both studies independently showed significance in terms of achieving resolution of symptomatic VMA. The pooled data showed a release rate of 26.5% in the ocriplasmin group compared with 10.1% in the placebo group. This led to the US Food and Drug Administration approval of ocriplasmin in 2012 for the treatment of symptomatic VMA. After intravitreal ocriplasmin, MH developed in 5.2% of patients (24/465), compared with 8.6% of patients (16/187) in the placebo group ($P = 0.15$).¹³ Fahim and Johnson¹⁴ (2014) reported a patient with VA loss, visual field constriction, pupillary abnormalities, attenuated retinal arteries, loss of outer retinal signals on spectral-domain OCT, and severely and acutely reduced electroretinogram (ERG) responses (B-waves were reduced more than A-waves) after intravitreal ocriplasmin injection. These authors postulated that enzymatic cleavage of intraretinal laminin is a biologically plausible mechanism for acute ocriplasmin retinal toxic effects. Similarly, Tibbetts and Witkin¹⁵ (2014) reported a patient with disruption of the photoreceptor inner segment–outer segment (ellipsoid) layer on spectral-domain OCT, and reduced ERG amplitudes correspond with an ocriplasmin recipient's symptoms of darkened vision. These authors postulated that ocriplasmin may have a diffuse enzymatic effect on photoreceptors or the retinal pigment epithelium that is not limited to areas of VMA. Hahn and the ASRS Therapeutic Surveillance Committee¹⁶ (2015) reported that a higher percentage of side effects occurred in 999 eyes in a premarketing clinical trial program compared with 4387 eyes in the postmarketing survey. Various side effects reported among eyes in the premarketing clinical trial program and eyes in the postmarketing survey included acute decrease in VA in 7.7% and in 1.3% of 4387 eyes; dyschromatopsia was observed in 1.6% and 0.5% of eyes; retina tear/detachment in 1.9% and 0.4% of eyes; lens subluxation/phacodonesis in 0.2% and 0.02% of eyes; and impaired pupillary reflex in 0.5% and 0.3% of eyes, respectively. However, Hahn et al acknowledge in their paper that voluntary postmarketing reporting grossly underestimates the incidence of adverse drug effects. The Macula Society Collaborative Retrospective Study of Ocriplasmin for Vitreomacular Traction reviewed 208 eyes with VMT, including 75 eyes with MH, with 1 month follow-up (Lim JJ, Glassman AR, Aiello LP, et al. Macula Society Collaborative Retrospective Study of Ocriplasmin for Vitreomacular Traction. ARVO 2016, Seattle, May 2, 2016. Abstract Number: 1805). After treatment for VMT, the VMT resolved in 45% of eyes by 1 week, 43% of eyes by 1 month, 58% of eyes by 12 weeks, and 74% of eyes at the final visit. The ERGs were performed in 9 eyes, 8 of which had MH. The ERG was severely diminished in 3 of 9 eyes 1 to 2 days after ocriplasmin administration compared with baseline. Two eyes showed no change in the ERG at 4 weeks but improved on the ERG by 12 weeks. One eye had persistent ERG changes at 18 months. The ERG was reported as showing minor to no change in the 6 other eyes. Seven eyes (5%) with no prior record of MH developed an MH, 3 (1.4%) developed a retinal tear, 6 (2.9%) reported retinal pigment epithelium changes and 4 eyes (1.9%) developed a retinal detachment. At the last follow-up visit, 10 eyes (4.5%) had undergone cataract surgery and 1 eye (0.5%) underwent a scleral buckle procedure. There were no cases of posttreatment endophthalmitis. The authors

concluded that with intravitreal ocriplasmin adverse events were not infrequent, but were mostly not serious.

The Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) Study by Tolentino et al (2014), a phase IIIb, 24-month, randomized, double-masked, multicenter study with optional cross-over treatment with a single intravitreal injection of ocriplasmin 0.125 mg, reported VMA/VMT resolution at day 28 in 41.7% of the ocriplasmin group versus 6.2% of the control sham group ($P < 0.001$), confirming ocriplasmin efficacy for the treatment of VMT/VMA patients (Tolentino M; OASIS Study Group. Long-term clinical outcomes with ocriplasmin: the OASIS study-baseline demographics and ocular characteristics. Invest Ophthalmol Vis Sci 2014;55:305. ARVO Annual Meeting Abstract). Improvement in best-corrected VA from baseline at month 24 (2 lines) was reported in 50.5% (95% confidence interval, 42.4–58.5) of the ocriplasmin group versus 39.1% (95% confidence interval, 28.3–49.9) in control sham group in the OASIS clinical trial (Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole; www.clinicaltrials.gov identifier, NCT01429441). No statistical analysis was provided for this outcome. Sadda et al (2016) presented the initial results of the OASIS MP-1 substudy to look at the effects of ocriplasmin and VMT/symptomatic VMA resolution on visual fixation and macular sensitivity using microperimetry (Sadda SR, Kozma-Wiebe P, Meunier E. The OASIS MP-1 substudy: characterization of the effect of ocriplasmin on microperimetry parameters. ARVO 2016, Seattle, May 2, 2016. Abstract Number: 1805). The study evaluated 27 of 220 patients who were enrolled in the larger OASIS trial. Short-term results of the OASIS MP-1 substudy suggest that, in the ocriplasmin group, fixation and sensitivity parameters tended to be better than in sham group over time.

In addition, ALG-1001, an integrin antagonist, is being evaluated for the management of VMT. Kuppermann et al (2016) conducted a prospective, double-masked, placebo-controlled, phase II clinical study, performed in 106 patients with symptomatic focal VMA across 20 sites in the United States and Europe. This study reported that 65% of patients treated with a 3.2-mg dose of ALG-1001 achieved release of VMA or VMT by 90 days (Kuppermann BD, Boyer DS, Kaiser PK, et al. Topline results from prospective, double-masked, placebo controlled phase 2 clinical study evaluating Luminate (ALG-1001) in patients with symptomatic focal vitreomacular adhesion. ARVO 2016, Seattle, May 2, 2016. Abstract Number: 1809). This study demonstrated that ALG-1001 was well-tolerated in all dosing groups. No safety issues were identified.

The clinical course of VMT based on observation only may be associated with spontaneous release of traction. Punjabi et al¹⁷ (2007) reported closure in stage 2 idiopathic FTMHs with VMT as documented by OCT. John et al¹⁸ (2014) reported a noncomparative case series (3 medical centers) of 106 eyes that were managed by observation alone. The patients with VMT noted on spectral-domain OCT were selected by the individual physician and were not part of a prospective study. The patients with fellow-eye MH and patients with advanced macular diseases such as diabetic macular edema and wet age-related macular degeneration were excluded from the study. The study eyes were graded using an OCT-guided anatomic classification. The term “grade” was specifically chosen because it does not imply sequential

progression, as opposed to the term “stage.” Grade 1 was incomplete separation of cortical vitreous with foveal attachment. Grade 2 was grade 1 with any intraretinal cyst, cleft, or schisis. Grade 3 was grade 2 with neurosensory elevation of the retina from retinal pigment epithelium (subretinal fluid). Tzu et al¹⁹ (2015) reported results of 230 eyes (185 patients) from 6 medical centers, including the updated data set of the paper from John et al.¹⁸ The mean initial and final best-corrected VAs were 20/55 (range, 20/20–20/400) and 20/51 (range, 20/20–20/400), respectively. Spontaneous release of VMT during the mean follow-up of 32 months occurred in 73 of 230 of study eyes (31.7%). The time to spontaneous release on OCT was a mean of 18 months (median, 10.9 months). During the course of the study, PPV was performed in 10 eyes: 6 of 230 for MH (2.6%), 2 for grade 2 VMT, and 2 for grade 3 VMT. In this subgroup of eyes undergoing PPV, 8 of 10 eyes had VA >20/40 at the last follow-up. In another retrospective study of patients with FTMH in 1 eye and “stage 0” MH (VMA or VMT by OCT testing) in the fellow eye, Chan et al²⁰ (2004) reported that the rate of developing FTMH in the fellow eyes was 4.3% (3/67) in patients with no abnormal vitreoretinal interface, 25% (1/4 cases) in patients with severe vitreoretinal anatomic alterations, and 50% (4/8 cases) with mild vitreoretinal anatomic alterations at baseline. These findings highlight the differences in the rates of progression of VMA/VMT in patients with FTMH in the fellow eye in comparison with patients with a normal fellow eye. It is important to recognize the clinical course of the progression because it may be preferable to select a nonobservational approach for patients with FTMH in the fellow eye.

Discussion

In this overview of management options for VMT, the pros and cons of each approach have been discussed. Pars plana vitrectomy achieves consistent and predictable release of VMT but has a low risk of postoperative FTMH. After additional surgery for the FTMH, hole closure and favorable visual outcomes can usually be achieved. Pneumatic vitreolysis is a relatively new, reportedly effective, and minimally invasive approach to achieve nonsurgical release of VMT. This approach of pneumatic vitreolysis seems to be the most cost-efficient and has few reported complications. Enzymatic vitreolysis is a nonsurgical approach for releasing VMA but has a high cost and frequent, although usually transient, side effects. Clinical trials have shown the effectiveness of this nonsurgical enzymatic vitreolysis approach compared with saline injection. Using observation alone, the untreated clinical course is often favorable in patients without FTMH in the fellow eye. Approximately 35% of patients in selected series will have spontaneous resolution of VMT and achieve stable or improved VA. Using observation, rates of progression to FTMH are low, but symptoms of visual disturbance may persist in untreated patients with VMT. In patients with FTMH in the fellow eye, observation can be considered for the management of VMT in the second eye, but the course of these fellow eyes with VMA/VMT has not been well-studied.

In conclusion, individual patient management can be based on the specific patient's clinical findings, potential risks, probable benefits, and costs of each option.

The physician should consider the patient's visual needs and visual disability in deciding between observation and treatment. In addition, the physician should consider the patient's general health, including cardiovascular disease requiring anticoagulation or ocular diseases

possibly increasing after treatment. Finally, the physician should consider the time requirements and imposition to the family members to comply with more complex treatment options. Analysis of evidence-based outcomes data from ongoing clinical trials and future research will add to our ability to make the best decisions for VMT patients.

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Abbreviations and Acronyms

ERG	electroretinogram
FTMH	full-thickness macular hole
MH	macular hole
OCT	optical coherence tomography
PPV	pars plana vitrectomy
PVD	posterior vitreous detachment
VA	visual acuity
VMA	vitreomacular adhesion
VMT	vitreomacular traction

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Figure 1.
Dr Charles L. Schepens.

Figure 2. Vitreomacular traction with surface retinal distortion, intraretinal cystic changes, and distortion of the ellipsoid zone on optical coherence tomography.