

Management of Refractory DME

The posterior hyaloid is the beginning of the decision-making process.

BY TAREK S. HASSAN, MD

While the management of many types of retinal disease has become more straightforward in recent decades, the treatment of chronic diabetic macular edema (DME) has become more difficult.

In the past, the management choices were easy, although not always successful: The choice was between observation and laser photocoagulation. Today, management of chronic DME has become one of the biggest day-to-day challenges for the retina specialist. This has happened for good reasons. We understand the disease better, we have better technologies to visualize DME, and we have more treatment options. Unfortunately, this is also for bad reasons, as sometimes our treatments do not work, and the edema remains refractory.

Our understanding of the pathogenesis of DME has improved. We know that hyperglycemia leads to increased free radical activity and other sequelae that result in osmotic damage and ultimately capillary epithelial damage, leading to DME. The knowledge that vitreomacular or epimacular traction contributes to DME over time also helps to frame our approaches to the disease.

Improved diagnostic tools have given us better ways to see DME. Spectral-domain optical coherence tomography (SD-OCT), high-resolution fluorescein angiography (FA), and widefield FA are complementary technologies that provide greater understanding and visualization of persistent and recurrent pathology in recalcitrant DME.

Most ophthalmologists have developed some type of paradigm for the treatment of chronic DME patients. This generally consists of some combination of laser, intravitreal injection of anti-VEGF or corticosteroid therapy, and vitrectomy, in concert with systemic control of diabetes. How does one ultimately decide which treatment to apply in what order? In this article, I present my approach to this question in a manner that seems logical to me.

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IMPORTANCE OF POSTERIOR HYALOID STATUS

When faced with a patient with a recalcitrant disease such as chronic DME, my goal is to find a management pathway that will maximize success and minimize failure. For me, the decision point at which management branches in 1 direction or another is based on assessment and management of the posterior hyaloid.

That is, in a given patient, I try to establish whether the posterior hyaloid is taut. If the hyaloid is not taut, then medical therapy, laser, or even observation is reasonable. If it is taut, and traction in any direction (anteroposterior, tangential, or both) can be demonstrated after a vigilant search, then I try to relieve the traction, either surgically or with a pharmacologic adjunct.

Others may use different decision points when choosing therapy for chronic DME, such as whether the edema is responsive to anti-VEGF therapy. However, there are too many variables with this approach. A positive response to anti-VEGF therapy may be short-lived, leading to the treadmill of multiple repeat injections. With a negative response, we may nevertheless treat with more anti-VEGF therapy, or try intravitreal triamcinolone acetate, laser, or vitrectomy. But we may not learn

anything about the reasons we succeed or fail if our first decision point is the response to anti-VEGF therapy.

Other potential decision points—whether the DME is focal or diffuse, whether there are microaneurysms or not, whether it is acute or chronic, proliferative or non-proliferative—are also unhelpful because each of those differentiating factors have multiple variables associated with them.

Assessment of the posterior hyaloid in chronic DME allows the most targeted, definitive intervention for the treatment of a specific pathophysiologic process.

ROLE OF VITRECTOMY

Given a patient with what I believe to be a taut posterior hyaloid, the next question is how to relieve the traction. Twenty years of data show that vitrectomy works in some eyes. In an eye with a taut hyaloid, vitrectomy with membrane peeling and removal of the posterior hyaloid, with or without peeling of the internal limiting membrane (ILM) and with or without panretinal photocoagulation (PRP), leads to relief of posterior hyaloidal traction. With this approach, visual improvement is possible in certain eyes once thought to be refractory to treatment.

The real-world approach to vitrectomy for DME has changed over time. In the era before widespread use of intravitreal injections, prior to 2005, vitrectomy appeared to be useful in most studies.

In multiple trials published from the early 1990s to 2000, in eyes with DME that had clinically visible or OCT-documented taut posterior hyaloidal traction, nearly all described visual acuity and anatomic improvement. Visual acuity improvement of more than 2 lines was reported in 49% to 92% of eyes in these studies, and resolution of clinically significant DME in 45% to 82% of eyes. More controversial were the results in eyes without clearly visible posterior hyaloidal traction (invisible or anteroposterior traction) in a group of studies published from 1996 to 2005. In these studies, visual acuity improvement of more than 2 lines was seen in 38% to 71% of eyes, and resolution of clinically significant CME in 43% to 100%.

Significantly improved visual acuity and anatomic outcomes after vitrectomy often came early and were long-lasting, although significant or complete resolution of DME could take 3 to 6 months.

We reviewed our results of vitrectomy in 45 eyes of 38 patients with refractory DME, with a mean follow-up of 56 (range, 31–94) months (unpublished data). At the last follow-up visit, 71% of eyes had stable or improved vision compared with preoperative status. Other studies confirm the long-lasting effect of vitrectomy.^{1,2}

MECHANISMS OF ACTION OF VITRECTOMY

There are potentially numerous mechanisms of action at work that explain how vitrectomy can improve DME. Successful surgery relieves anteroposterior vitreoretinal traction by creating a posterior vitreous detachment (PVD). Nasrallah and colleagues showed many years ago that DME is less common in eyes with PVD than in those with no PVD.³ Hikichi et al,⁴ a decade later, showed that DME spontaneously resolved more often in eyes with PVD (55%) than in eyes with no PVD (25%). The procedure also relieves tangential traction. Histologic studies have shown that there are contractile vitreous and RPE cells in multilayer sheets on posterior hyaloid membranes removed from eyes with DME.

Vitrectomy can also relieve vitreoschisis, in which a split portion of the posterior hyaloid remains after peeling of the hyaloid, with appearance and staining characteristics similar to those of the ILM. This is a common occurrence in eyes with DME and is often underestimated.

Numerous small, uncontrolled studies suggest that there are anatomic and visual benefits due to removal of the ILM in vitrectomy. ILM removal ensures that the posterior hyaloid has been removed, especially in an eye with vitreoschisis, and it likely reduces the likelihood of post-vitrectomy epiretinal membrane (ERM) formation. This step also ensures removal of any intrinsically pathologic ILM. The ILM in eyes with chronic DME contains increased levels of fibronectin, laminin, and types I, III, IV, and V collagen. Peeled ILM specimens from DME eyes show extensive collagen on the vitreous side and are 2.5 to 3 times thicker than ILM peeled in eyes with other pathologies, such as macular hole. This intrinsically contractile membrane may affect fluid flows across the retina that contribute to the edema, and therefore its removal is beneficial.

Vitrectomy also removes numerous vasopermeable factors such as VEGF, sICAM-1, interleukin-6, and other molecules that are elevated in eyes with DME from the vitreous cavity.

Holekamp and colleagues⁵ showed that vitrectomy increases oxygenation in the vitreous cavity up to 10 times in a long-lasting fashion. PRP at the time of vitrectomy also reduces midperipheral ischemia, which may reduce VEGF and other vascular permeability factors in the vitreous cavity as well.

BENEFITS OF VITRECTOMY

Eyes with obvious anteroposterior hyaloidal traction on OCT seem to reap the greatest benefit from vitrectomy. Also deriving benefit, but perhaps less so, are eyes with obvious tangential traction on OCT, and these, in turn seem to benefit more than eyes that have no obvi-

ous OCT evidence of traction but do have a clinically visible opacified hyaloid. Other clinical features of eyes that have beneficial outcomes from vitrectomy include short duration of DME, little or no macular ischemia, mild or no preoperative laser, no foveal hard exudates, good (or bad) preoperative visual acuity (depending on the trial), and an obviously taut posterior hyaloid or ERM for removal.

Most published trials of vitrectomy for DME show positive short- and long-term results, but some do not. Why are there conflicting results? The answers have to do with trial design. There are many variables in this disease, with a heterogeneous population, complex disease characteristics, and individual variations in surgical technique.

To truly assess the effect of vitrectomy on DME, a study would have to define patient characteristics; define and determine what “traction” is; define and determine the amounts of macular ischemia, RPE atrophy, and choroidal ischemia present; and define the surgical indications, parameters, and techniques to be used. Published studies of vitrectomy for DME are rarely, if ever, written so that these variables are comparable.

A trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net) illustrates the problems investigators face in reporting data on vitrectomy in DME.⁶ The DRCR.net is a wonderful organization responsible for many large-scale clinical studies that have answered numerous important questions, but the DRCR.net vitrectomy for DME trial is not 1 of them. The study includes results of vitrectomy in 87 eyes with DME and vitreomacular traction from 35 US sites, which is, on average, a little over 2 patients per site. The presence of vitreomacular traction was based on investigator assessment alone. Vitrectomy was performed according to the investigator’s usual routine; the only defined surgical guidelines were the creation of 3 sclerotomies, peeling of the posterior hyaloid, removal of any ERM present, and examination of the peripheral retina.

The investigators found that retinal thickening was significantly reduced in most eyes, visual acuity improved by 10 letters or more in 38% of eyes and worsened in 22% of eyes, and there was a low operative complication rate.

This trial was only a prospective data collection study—basically, a survey—not a randomized, controlled trial. There was no standardization of indications, surgical procedure, or technique. No substantive conclusions regarding vitrectomy for chronic DME can be drawn from this study other than it works for some eyes and that a large, prospective, multicenter, randomized clinical trial with extensive inclusion and exclusion criteria

is needed to better assess the efficacy of vitrectomy for DME in a variety of situations.

Clearly, however, vitrectomy has a role in the management of this disease because it provides long-term efficacious treatment in some eyes with refractory, clinically significant DME. It can stabilize or improve outcomes in eyes that have not responded to other treatments. The key is to determine which eyes will benefit, and the best way to do this at present is to critically evaluate the vitreomacular interface with SD-OCT and search vigilantly for tangential posterior hyaloidal traction. This traction is often subtle, not clinically visible, and difficult to see, even on OCT.

ENZYMATIC VITREOLYSIS

Enzymatic vitreolysis shows promise to achieve some of the benefits of vitrectomy without surgery. This non-surgical modality has been covered quite thoroughly recently with the regulatory approval earlier this year of a proteolytic enzyme, ocriplasmin (Jetrea, Thrombogenics Inc), for the treatment of symptomatic vitreomacular adhesions and macular hole. Plasmin and ocriplasmin are nonspecific proteases that cause dose-dependent degradation of glycoproteins, leading to liquefaction of the vitreous and pharmacologic separation of the posterior vitreous from the ILM.

More than a decade ago, Williams and colleagues⁷ showed that, with administration of autologous plasmin during vitrectomy in DME, intraoperative creation of a PVD was easier, and better visual acuity resulted. Other investigators reported similar findings.⁸

This led to the proposal that perhaps vitrectomy could be avoided entirely through the intravitreal administration of plasmin. Diaz-Lopez and colleagues⁹ evaluated the effect of intravitreal injection of autologous plasmin without vitrectomy in 16 eyes of 16 patients, using the unoperated fellow eyes as controls. The plasmin-treated eyes had significant reduction of DME and improved visual acuity outcomes compared with controls.

ROLE OF INJECTIONS

We have been living in the era of intravitreal injections in recent years, especially since 2005. Intravitreal injections of anti-VEGF agents and intravitreal triamcinolone can be highly effective against DME. However, still to be determined are how long to treat with these drugs and where other treatments fit into our injection regimens. Are injections a panacea for all refractory DME, or can they actually be detrimental to our results?

A host of large-scale clinical studies have shown the benefits of numerous anti-VEGF agents in the treatment of DME. A partial list includes the BOLT, DRCR.net, and PACORES studies with bevacizumab (Avastin,

Genentech); READ 2, RISE, RIDE, RESOLVE, RESTORE, and DRCR.net studies with ranibizumab (Lucentis, Genentech); and the DAVINCI study with aflibercept (Eylea, Regeneron Therapeutics).

To skim a few top-line results of these trials, in the BOLT trial comparing intravitreal bevacizumab with macular laser in 80 eyes, at 12 months there was a mean change in visual acuity of +8 letters in the injection group and -0.5 letters in the laser group.¹⁰

The RISE and RIDE phase 3 clinical trials compared 2 doses of ranibizumab to sham injection in 377 and 382 subjects, respectively.¹¹ At the 24-month endpoint, 45% of patients in the ranibizumab 0.3 mg group and 39% in the ranibizumab 0.5 mg group gained 3 or more lines of visual acuity, compared with 18% in the sham group. Mean changes in best corrected visual acuity (BCVA) were +12.5 letters in the 0.3 mg group, +11.9 in the 0.5 mg group, and +2.6 in the sham group.

The DAVINCI phase 2 study compared laser with multiple doses and dosing schedules of aflibercept.¹² At 24 months, changes in BCVA in 4 aflibercept groups ranged from +8.5 to +11.4 letters, compared with +2.5 in the laser group. Notably, no statistically significant differences were seen among the groups that received aflibercept—including those who received injections at 8-week and 4-week fixed intervals.

The mechanical effects of intravitreal injections include the creation of spontaneous PVD in some eyes. Control eyes receiving sham injections in the ocriplasmin trial and other studies have shown increased rates of PVD formation in eyes receiving injections of a variety of agents. It is very likely that in some cases, the intravitreal injection regimen creates a PVD that thereby assists in the reduction of DME.

Options for long-term delivery of corticosteroids have been explored in DME. The only sustained-release device currently approved in the United States, for any use (not DME), is the dexamethasone implant (Ozurdex, Allergan). A phase 2 trial in 171 eyes compared implants in 2 doses (350 µg and 700 µg) with observation in eyes with chronic DME.¹³ At 90 days, BCVA improved by 10 or more letters in 33% of eyes with the 700 µg implant, compared with 21% with the smaller dose and 12% with observation. Statistically significantly greater improvement in central foveal thickness was seen in treated eyes than in observed eyes. The effect was lost at about 180 days. Complications of increased intraocular pressure and cataract were seen in treated eyes. Additional trials are under way to generate longer-term data, and this implant is being reviewed for potential FDA approval for use in the treatment of DME in the future.

MICROPULSE LASER

Micropulse laser has been proposed as an alternative to standard thermal laser for treatment of DME. Microsecond pulses of laser purportedly allow the treated tissue to cool between pulses, reducing thermal buildup and confining the thermal effects to a limited area. Reports indicate that good patient outcomes can be achieved without the thermal damage seen with traditional laser.¹⁴

SYSTEMIC HEALTH

We can never forget the importance of control of systemic health in diabetic patients. Persistent clinically significant DME correlates with elevated blood sugar, elevated lipid levels, and hypertension, and with depressed renal status. Do and colleagues¹⁵ found that hemoglobin A1c levels were elevated in 74% of patients with significant DME, compared with 12.5% of those without DME. Deak et al¹⁶ found that increased vision-threatening diabetic retinopathy and severe hard exudates were associated with high baseline caloric intake and sodium level.

CONCLUSIONS

As noted above, most retina specialists have a mental paradigm in mind for the treatment of patients with chronic DME. I believe that, at present, the standard of care for these patients is combination therapy. For patients with DME, I think about managing the posterior hyaloid, and multiple branches of a decision tree descend from that first basic determination.

First, determine whether there is traction. Once you decide this in a definitive manner, you can plan a course of treatment. Multiple additional considerations will refine the treatment pathway.

Clinically significant DME is a complex condition, and when it is refractory it cannot be approached by choosing only 1 treatment directed at 1 mechanism. Trials that compare multiple treatments must control for all other variables to determine whether 1 works better than another, but most trials do not do that.

We have learned a lot about DME. We have many diagnostic tools for evaluation and a variety of therapeutic tools with which to attack it. Future therapies, such as sustained-release devices and micropulse laser, are interesting and potentially promising. The Holy Grail would be a method to improve or reverse macular ischemia.

We must evolve in our thinking about DME. The understanding of clinically significant DME, as defined by the ETDRS, has changed, and this is no longer a clinically useful term. Macular laser alone is no longer the gold standard of treatment; it is too simplistic for our current understanding of DME.

Management of the posterior hyaloid is not just about vitrectomy. It is clear that, in DME, a PVD is good. Whether there is more benefit in generating the PVD via vitrectomy or another method is unclear, but however we achieve that PVD, it works. Posterior hyaloid management, in my opinion, is vital to the understanding, control, and treatment of this chronic condition. ■

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1. Kralinger MT, Pedri M, Kralinger F, Troger J, Kieselbach GF. Long-term outcome after vitrectomy for diabetic macular edema. *Ophthalmologica*. 2006;220(3):147-152.
2. Mochizuki Y, Hata Y, Enaida H, et al. Evaluating adjunctive surgical procedures during vitrectomy for diabetic macular edema. *Retina*. 2006;26(2):143-148.
3. Nasrallah FP, Jalkh AE, Van Coppenolle F, et al. The role of the vitreous in diabetic macular edema. *Ophthalmology*. 1988;95(10):1335-1339.
4. Hikichi T, Fujio N, Akiba J, Azuma Y, Takahashi M, Yoshida A. Association between the short-term natural history of diabetic macular edema and the vitreomacular relationship in type II diabetes mellitus. *Ophthalmology*. 1997;104(3):473-478.
5. Holekamp NM, Shui YB, Beebe DC. Vitrectomy surgery increases oxygen exposure to the lens: a possible mechanism for nuclear cataract formation. *Am J Ophthalmol*. 2005;139(2):302-310.
6. Diabetic Retinopathy Clinical Research Network Writing Committee; Haller JA, Qin H, Apte RS, et al. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. *Ophthalmology*. 2010;117(6):1087-1093.e3.
7. Williams JG, Trese MT, Williams GA, Hartzler MK. Autologous plasmin enzyme in the surgical management of diabetic retinopathy. *Ophthalmology*. 2001;108(10):1902-1905.
8. Azzolini C, D'Angelo A, Mastranzi G, Codenotti M, Della Valle P, Prati M, Brancato R. Intravitreal plasmin enzyme in diabetic macular edema. *Am J Ophthalmol*. 2004;138(4):560-566.
9. Diaz-Llopis M, Udaondo P, Arevalo F, et al. Intravitreal plasmin without associated vitrectomy as a treatment for refractory diabetic macular edema. *J Ocul Pharmacol Ther*. 2009;25(4):379-384.
10. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology*. 2010;117(6):1078-1086.e2.
11. Nguyen QD, Brown DM, Marcus DM, et al; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119(4):789-801.
12. Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The DA VINCI Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology*. 2011;118(9):1819-1826.
13. Haller JA, Kuppermann BD, Blumenkranz MS, et al; Dexamethasone DDS Phase II Study Group. Randomized controlled trial of an intravitreal dexamethasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol*. 2010;128(3):289-296.
14. Luttrull JK, Sramek C, Palanker D, Spink CJ, Musch DC. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. *Retina*. 2012;32(2):375-386.
15. Do DV, Shah SM, Sung JU, Haller JA, Nguyen QD. Persistent diabetic macular edema is associated with elevated hemoglobin A1c. *Am J Ophthalmol*. 2005;139(4):620-623.
16. Deák GG, Bolz M, Kriechbaum K, et al; Diabetic Retinopathy Research Group Vienna. Effect of retinal photocoagulation on intraretinal lipid exudates in diabetic macular edema documented by optical coherence tomography. *Ophthalmology*. 2010;117(4):773-779.

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