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MICROVASCULAR COMPLICATIONS—RETINOPATHY (DL CHAO AND G YIU, SECTION EDITORS)

Surgical Innovations in the Treatment of Diabetic Macular Edema and Diabetic Retinopathy

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Abstract

Purpose of Review Diabetic macular edema (DME) and complications of proliferative diabetic retinopathy (PDR) are the primary causes of vision loss in patients with diabetic retinopathy. As the incidence of diabetes increases worldwide, new, cost-effective treatments for DME and PDR will become paramount. Currently, anti-vascular endothelial growth factor (anti-VEGF) medications are considered first-line treatment. However, multiple visits for injections and the economic and time burden they entail make this treatment modality less than ideal. Early vitrectomy as well as depot delivery systems for medications could potentially reduce the treatment burden of patients with diabetes, prevent visual loss, and provide long-term stabilization of retinopathy in patients with diabetes. Newer port delivery systems for anti-VEGF medications could one day make this treatment modality better suited for patients across the globe.

Recent Findings Real-world data shows poor compliance with treatment among patients with diabetes. Recent publications show catastrophic results when anti-VEGF treatments are stopped abruptly. The port delivery system for ranibizumab shows maintenance of adequate anti-VEGF levels in the vitreous cavity for many months. Early vitrectomy can provide cost-effective long-term stabilization in eyes with diabetic retinopathy.

Summary Microincisional vitrectomy as a treatment for DME and PDR remains controversial and larger trials are needed to definitively prove its superiority over other modalities; however, small-scale data point towards its usefulness in specific populations. Newer port delivery systems of anti-VEGF show promise in decreasing the number of office visits in patients with diabetic retinopathy.

Keywords Diabetic macular edema · Diabetic retinopathy · Laser photocoagulation · Vitrectomy

Introduction

As of 2017, there were 425 million adults worldwide with diabetes and its incidence continues to increase [1]. In the USA alone, 33.9% of adults over 18 years had prediabetes in 2015 [2]. Complications of diabetes, namely diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) and its sequelae, are the global leading causes of blindness among people during their productive years [3]. However, considering the significance of the disease, there is a scarcity of large studies on the surgical treatment of the complications of diabetes. The only large-scale, randomized trial that has been performed, the Diabetic Retinopathy Vitrectomy Study (DRVS), is over 34 years old [4]. Since the DRVS, treatment of diabetic complications has evolved to include multiple modalities, including laser photocoagulation, pharmacologic treatment, and microincisional vitrectomy surgery (MIVS). Here, we summarize the current knowledge regarding treatment of DME and PDR and offer future directions to improve

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treatments, making them less burdensome and more effective, affordable, and long-lasting with minimal follow-up.

Prevention and optimal control of blood sugar levels are the ideal ways to prevent diabetic retinopathy and its ensuing visual compromise [3]. Nevertheless, many patients are diagnosed late and can present with advanced disease, necessitating effective treatments for diabetic complications. In a large cohort of patients newly diagnosed with diabetes, 13% were found to have diabetic retinopathy and 0.3% had proliferative disease [5]. In fact, patients with severe non-proliferative diabetic retinopathy (NPDR) and PDR have a prevalence of vision-related functional burden of 48.5% [6]. Diabetic macular edema is the principal cause of loss of vision among patients with diabetic retinopathy. The pathophysiology of PDR and DME and their associated visual loss stems primarily from multiple inflammatory cytokines, advanced glycemic age products, and the production of vascular endothelial growth factor (VEGF), leading to increased vascular permeability and damage resulting in leakage from blood vessels [7]. This leads to multiple complications including focal leakage from microaneurysms, diffuse leakage from vascular alterations, intraretinal edema, subretinal fluid with localized detachment, traction from a thickened attached hyaloid, vitreomacular traction, and localized tractional retinal detachment.

Laser Photocoagulation

Since the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Diabetic Retinopathy Study (DRS) in the 1980s, the mainstay of treatment of DME and PDR has been laser photocoagulation, namely focal and grid treatment for DME and panretinal photocoagulation (PRP) for PDR [8, 9]. Although effective in reducing visual loss by 50% compared with untreated patients, laser photocoagulation is not effective in improving vision and has significant long-term complications including growth of the scars with scotomas and a reduction of the visual field [8]. Also, despite PRP treatment, many PDR eyes progress to develop DME, vitreous hemorrhage, and tractional and rhegmatogenous retinal detachments. In Protocol S of the Diabetic Retinopathy Clinical Research Network (DRCRnet), despite initial PRP, many eyes continued to need multiple treatments of ranibizumab for DME [10, 11].

Pharmacologic Therapy

Recently, more physicians have advocated for the pharmacologic, particularly anti-VEGF, treatment of both DME and severe NPDR, as a number of studies have demonstrated reductions in both edema and progression of the retinopathy scores [12, 13]. Despite the success of anti-VEGF treatment, it fails to provide visual improvement in over 40% of eyes and residual edema remains in 31–66% of treated eyes [14–16]. This is not surprising, given the multifactorial nature of the disease and the failure of anti-VEGF to address the other cytokines such as interleukin-6 that contribute to the disease [7]. Additionally, this treatment modality carries the burden of monthly visits for injections and with costs of up to $20,000 per year for anti-VEGF treatments in the USA; patients may find it difficult to remain compliant with therapy. Non-compliance with visits when using pharmacologic treatment for diabetic retinopathy can pose catastrophic effects, including neovascular glaucoma, tractional retinal detachment (TRD), tractional and rhegmatogenous retinal detachment (TRRD), vitreous hemorrhage, and visual loss rates of more than 3 lines reported in 77% of eyes [17•] (Fig. 1). Considering that non-compliance rates with appointments in patients with diabetes are estimated to be up to 39%, treatment with anti-VEGF in patients with diabetes, particularly the employed and economically challenged, poses a number of difficulties and is a less than ideal treatment [18].

While the current recommended regimen of monthly injections and visits is unsustainable for most patients with diabetes, surgically implanted drug reservoirs may be a possible solution to increase duration of action. One such drug reservoir, the port delivery system with ranibizumab, has currently finished a phase 2 clinical trial, in patients with age-related macular degeneration (AMD) [19•]. In this system, a self-retaining port reservoir is surgically placed in the pars plana and is covered with tenons and conjunctiva. It can be refilled with ranibizumab in varying concentrations. At present, 10 mg/ml, 40 mg/ml, and 100 mg/ml doses have been studied in AMD and median time to first implant refill was 8.7, 13.0, and 15.0 months, respectively [19•]. The main complication seen was vitreous hemorrhage in 4.5% of eyes [19•]. While this implant is currently being studied for AMD, it could also be a promising treatment modality for the treatment of DME, PDR, and NPDR as it would dramatically reduce the number of required injections and visits for patients with diabetes and thus tackle non-compliance.

Protocol S of the DRCRnet compared PRP with monthly ranibizumab treatments for PDR [10, 11]. At 5 years, there was no difference in visual acuity between the ranibizumab and PRP arms of the study, with systemic and ocular adverse events comparable between the two groups [10]. When cost-effectiveness analysis was done in this study at 2 years, ranibizumab was cost-effective only for eyes that had DME associated with PDR but not for eyes with only PDR [20]. What is underscored in this study is the importance of compliance with patient visits for overall success of anti-VEGF treatments. At the 5-year outcomes, 34% of eyes were lost to follow-up, supporting other data showing that

Fig 1 Color fundus photographs. **a** 42-year-old patient with proliferative diabetic retinopathy presented with vision of 20/400 in the right eye (OD) and a large boat-shaped hemorrhage in the same eye. **b** Patient was followed and treated monthly with anti-vascular endothelial growth factor therapy with vision stable at 20/60 OD 3 months after presentation. **c** Patient was lost to follow-up due to a hospitalization and returned 4 months later with visual acuity of hand motion OD and massive reproliferative retinal detachment

the percentage of visits missed or canceled by patients with diabetes is significant [18].

Vitrectomy

Vitrectomy is another treatment option for DME and PDR, though its effectiveness differs between the two disease states. For PDR, early vitrectomy has been known to result in long-term stabilization of eyes ever since the DRVS, where eyes treated with early vitrectomy for vitreous hemorrhage had better outcomes [4]. This was particularly true in patients with type 1 diabetic retinopathy. Recent improvements in technology to evaluate and treat patients with diabetic retinopathy have increased our understanding of the disease and have improved outcomes and reduced complications. These include ultra-wide field angiography to evaluate peripheral ischemia and optical coherence tomography angiography to elucidate the foveal status as well as early neovascular formation. On the treatment side, improved visualization systems with wide angle viewing and 3D viewing during vitrectomy can reduce surgical times and lower complications from poor visibility. Modern vitrectomy machines with intraocular pressure control and valved cannulas to decrease intraoperative bleeding have reduced intraoperative complications. The use of preoperative anti-VEGF and small gauge systems, mainly 27 and 25g, has reduced the incidence of postoperative hypotony and vitreous hemorrhage and thus the need for reoperation in diabetic eyes undergoing vitrectomy [21]. Recently, data has been presented at various meetings showing improved long-term outcomes in eyes with only PDR treated with vitrectomy with removal of the posterior hyaloid and PRP. Removal of the posterior hyaloid in younger patients eliminates the possibility of some of the catastrophic consequences of PDR, namely the development of TRD and TRRD. Also, vitrectomy offers long-term stabilization of the disease for decades, which makes the treatment modality particularly attractive from a cost and compliance standpoint, particularly in people with diabetes who are younger and of working age (Fig. 2). Specifically, the cost of vitrectomy is low in many developing countries. In Indonesia, the average cost for vitreous surgery under general anesthesia for each patient was \$322.17, whereas for local anesthesia it was \$220.57 [22]. This makes vitrectomy an ideal treatment for people with diabetes, particularly when compared with the financial and time costs associated with treatment with anti-VEGFs.

Vitrectomy is more controversial in the treatment of DME without tractional components. A study of 45 patients with DME treated with vitrectomy showed a median improvement of visual acuity from 20/100 to 20/63 [23]. Similarly, a meta-analysis of vitrectomy for DME of 857 eyes showed visual acuity improvement in a significant proportion of eyes, particularly when internal limiting membrane (ILM) peeling was part of the procedure [24]. Nevertheless, other meta-analyses have shown no benefit of vitrectomy for DME in either functional or structural outcomes compared with focal laser photocoagulation at 12 months [25]. The wide variety of results seen throughout the many series published on the benefits of vitrectomy for DME underscore the heterogeneity of the patients included and the varied stages of disease, duration of the edema, and inconsistency of surgical maneuvers utilized [26, 27]. Another limitation of these studies is that most patients undergoing vitrectomy for DME in the published studies had a multitude of other unsuccessful treatment regiments before and vitrectomy was used as a last resort. As such, most patients in published series have a poor prognosis for resolution of edema given the many failed treatments and may have permanent neural damage to the photoreceptors from long-standing DME.

Previous reservations of vitrectomy for DME were a result of the complication rate of vitrectomy that was seen in the 20g vitrectomy era. Technological advances in vitrectomy with the introduction of MIVS and optimized vitrectomy platforms with fluid and pressure control have significantly reduced surgical complications in eyes undergoing vitrectomy. Significant complications of vitrectomy are around 1%, which is comparable to the cumulative serious complication rates of multiple anti-VEGF injections for many years [28, 29]. The possibility of reduced response to anti-VEGF after vitrectomy has also been used as an argument against vitrectomy for eyes

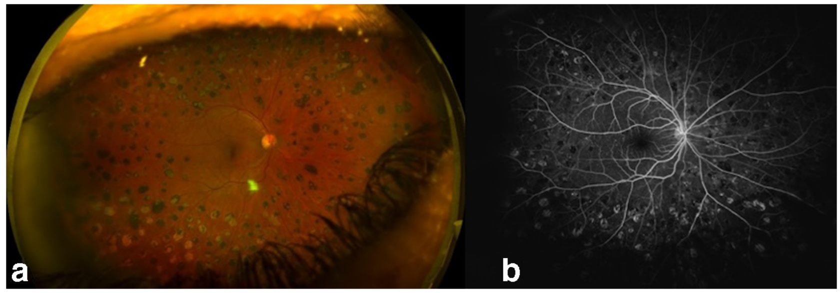

Fig 2 **a** Color fundus photograph and **b** fluorescein angiogram of the right eye of a male patient who underwent pars plana vitrectomy and intraoperative mild panretinal photocoagulation for vitreous hemorrhage 12 years prior. Visual acuity has remained 20/25 without any need for further treatments since the surgery

with DME. Nevertheless, data from the DRCRnet suggests that prior vitrectomy does not change the effectiveness of later anti-VEGF therapy [30].

There does seem to be consensus that eyes with DME caused by vitreomacular interface anomalies may benefit from surgery, and pars plana vitrectomy remains the first-line treatment in these eyes. Pathologies included are epiretinal membranes (ERM), vitreomacular traction and adhesion, a thickened hyaloid, localized foveal detachment from traction, or tractional retinal detachment. Vitrectomy with MIVS can be considered in eyes with significant edema, particularly in patients who have compliance issues, who may be unable to travel frequently to appointments or who cannot afford injections. Predictive factors of improved outcomes with vitrectomy have been studied, but no consensus has been reached due to the paucity of large comparative studies on vitrectomy for DME [31, 32]. Short duration of DME, lack of ischemia in the foveal region, and intactness of the external limiting membrane as shown by an intact ellipsoid zone are some of the factors that can be evaluated in the future to better select patients that will benefit from vitrectomy. Also, there is no consensus about the ideal ancillary steps to utilize during vitrectomy to optimize anatomical and functional results in eyes with DME. Removal of ERM is recommended but removal of the ILM remains controversial, with some studies showing a benefit [24]. The need for peripheral photocoagulation, intraoperative steroids at the conclusion of cases, or the use of air is inconclusive [23]. Large trials comparing anti-VEGF with vitrectomy for DME are needed, as more definite results are necessary to expand our understanding of the potential benefits of vitrectomy for DME. New guidelines and broadened indications should be devised for the use of vitrectomy for the treatment of diabetic complications, including diabetic macular edema and proliferative diabetic retinopathy.

Conclusions

Retinal specialists will be particularly challenged in the upcoming decades with the explosion of obesity and type 2 diabetes worldwide, and the economies of many countries will be strained to provide treatment for the resulting complications. Nevertheless, there has been great progress from the original trials on photocoagulation in the 1980s for the treatment of DME and PDR. There are now effective pharmacotherapies with anti-VEGF treatments; however, these are not ideal for all patient populations given the cost and time requirement involved. Future technologies such as the port delivery system may mitigate these barriers for patients. Early vitrectomy with modified PRP and hyaloid removal in eyes with severe NPDR and PDR is an attractive treatment modality, particularly in younger patients (Video 1). With improvements in vitreous surgery with MIVS leading to reduced complications and shorter surgical times, this may well be the most cost-effective treatment, particularly in countries where the surgical costs are low. Nevertheless, before this treatment can be recommended, a randomized clinical trial is necessary to validate its functional, anatomic, and cost benefits. New guidelines and indications for the various treatment modalities for DME and PDR should be devised, as medical knowledge and technical advancements have made great progress in the field since the only two large-scale, randomized trials for diabetic complications, the ETDRS and the DRS.

Compliance with Ethical Standards

Conflict of Interest Maria H. Berrocal has obtained speaker fees from Allergan and Alcon. Luis A. Acaba and Megan L. Chenworth declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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