Should We Consider Pars Plana Vitrectomy in the Primary Treatment of Diabetic Macular Edema?

Abstract

Diabetic macular edema (DME) is the most common cause of moderate visual loss in diabetic patients. The current treatment of choice for DME is anti-VEGF treatment. Even though recent clinical trials have shown that anti-VEGF treatment is superior to laser photocoagulation there are certain concerns regarding its sustainability over the long term. Most patients that undergo pharmacological inhibition with anti-VEGF agents need multiple monitoring visits that include OCT imaging and multiple injections. There is a theoretical concern regarding systemic thrombo-embolic events with chronic VEGF suppression.

Pars plana vitrectomy (PPV) by increasing the vitreous cavity oxygenation, relieving vitreomacular traction and removing cytokines from the vitreous cavity may cause long term resolution of DME without the aforementioned concerns.

Keywords: diabetic macular edema; VEGF; pars plana vitrectomy; oxygen; ranibizumab; bevacizumab; aflibercept; laser photocoagulation; vitreomacular traction; diabetic retinopathy

Introduction

The global incidence and prevalence of diabetes mellitus (DM) have reached epidemic proportions. According to estimates of the World Health Organization, by the year 2030 there will be 360 million people worldwide affected with DM.1 DM is no longer a disease of rich developed countries. Changes in dietary habits, obesity and physical inactivity are responsible for spreading this epidemic into the developing countries.1 All of these individuals will be at risk of developing diabetic retinopathy (DR).

DR is a progressive condition characterized by microvascular alterations that lead to retinal ischemia, an increase in retinal vasopermeability, retinal neovascularization and macular edema.2, 3 If left untreated patients with DR can suffer severe visual loss.4 In developed countries DR constitutes the leading cause of blindness in the working age population5 and has a considerable economic impact on society especially on healthcare systems.6-8 Since the introduction of panretinal photocoagulation into routine clinical practice, the rate of severe visual loss has dropped tremendously in developed countries. Diabetic macular edema (DME) remains the most common cause of moderate visual loss in diabetic patients.9

DME is characterized by an excessive vascular permeability that leads to an extravasation of plasma constituents and accumulation of extracellular fluid in the inner retina.10 The pathogenesis of DME is multifactorial and several molecules such as prostaglandins, leukotrienes, protein kinase c, nitric oxide, vascular endothelial growth factor (VEGF) and tumor necrosis factor (TNF) a have been implicated in the development of DME.11 Of these VEGF appears to be one of the most important ones. These recent advances have fueled an interest in the pharmacological treatment of DME.

Current Treatment

Until recently macular laser photocoagulation was the treatment of choice for DME. The ETDRS showed that in eyes with DME, focal or grid macular photocoagulation reduced moderate visual loss by 50%. However only 17% had some visual gain and less than 3% had a significant gain after 3 years of
follow-up. Several recent randomized clinical trials have shown that anti-VEGF agents outperform macular laser photocoagulation and have become first line agents in the treatment of DME. Up to 40% of eyes treated with monthly ranibizumab for 36 consecutive months gained ≥ 3 lines of best-corrected visual acuity (BCVA). The 2014 Preferences Survey of the American Society of Retinal Specialists (www.ars.org/pat-survey) show that a vast majority of vitreoretinal specialists prefer to use anti-VEGF agents as their first line treatment in eyes with center involved DME.

Despite the benefits shown by pharmacological inhibition of VEGF in eyes with DME, there are several concerns that need to be addressed. Most eyes require multiple injections to achieve the best visual outcomes. Pharmacological treatments are expensive and represent an important economic burden. In many parts of the world, particularly in the developing countries, chronic anti-VEGF therapy for DME is not sustainable in the long term. The multiple visits also impose a burden on the caretakers and patients themselves. There is a theoretical increased risk of systemic thromboembolic events with these drugs. There is no doubt that an intravitreal injection of an anti-VEGF drug reaches the systemic circulation. However, whether or not it increases the risk of systemic thromboembolic events remains controversial. Therefore, alternate therapies need to be developed.

**Hypothesis**

We propose that primary PPV should be explored as a treatment option in the primary management of DME. PPV may cause resolution of DME by several mechanisms. DME may be secondary to both anterior-posterior and tangential tractional forces on the macula. PPV eliminates traction by peeling the posterior hyaloid, epiretinal membranes and internal limiting membrane (ILM). Hypoxia is a major driver of VEGF secretion thus alleviation of hypoxia causes VEGF downregulation. Since PPV increases the oxygen concentration in the vitreous cavity, it may also downregulate VEGF secretion. Finally, PPV clears the vitreous cavity of cytokines and allows a faster clearance of newly secreted cytokines such as VEGF.

**Discussion**

The molecular pathways involved in the pathogenesis of DME have been elucidated in part. VEGF plays a central role. The RISE and RIDE trials have shown that continuous VEGF suppression is beneficial in eyes with DME. Unlike macular laser photocoagulation where only a small percentage of eyes had an improvement in vision, monthly treatment with ranibizumab for 3 years improved the BCVA in 40% of patients. Similarly, the Diabetic Retinopathy Clinical Research network has shown that eyes that were treated with ranibizumab coupled to deferred macular photocoagulation gained an average of 9.7 letters at 3 years. In comparison, eyes that were treated with macular laser photocoagulation gained on average just 2 letters. These results have changed the treatment algorithm of DME. Currently, anti-VEGF drugs are the preferred first line treatment of center involved DME.

There is no doubt that intravitreal anti-VEGF drugs have been a great advancement in the treatment of DME. However, there are several concerns regarding their use. To fully achieve the complete benefits of anti-VEGF therapy, most patients require multiple monitoring visits and injections over the years. The calculated cumulative risk of endophthalmitis after 20-40 injections has been calculated to be around 1%. There are also economic considerations. Smiddy analyzed the economic costs of the different treatments available for DME. Not surprisingly anti-VEGF therapy is very expensive. A cheaper alternative is needed and PPV may be considered such an alternative therapy.

PPV alleviates DME through multiple mechanisms. These mechanisms include elimination of tractional elements, improvement of intravitreal oxygenation, removal of pathological cytokines from the vitreous cavity and acceleration of the half-life of intravitreal cytokines.

Prior to the invention of the optical coherence tomography, precise clinical evaluation of the vitreous was difficult due to its transparency. The El Bayadi-Kajitura lens was designed to evaluate the vitreous during slit lamp biomicroscopy. Nasrallah et al were the first to suggest that the vitreous might play a role in the pathogenesis of DME. They used this lens to compare the rate of posterior vitreous detachment (PVD) in eyes with DME to those without DME. They found that PVD occurred in 20% of patients with DME as opposed to 55% in those without DME, suggesting that the attached posterior hyaloid might be exerting traction on the macula and contributing to the DME. Hikichi and colleagues followed prospectively a cohort of eyes with DME for 6 months. In this group of patients, 55% of cases had spontaneous resolution of their DME upon posterior vitreous separation. In contrast only 25% of cases without PVD had DME resolution. Lewis and colleagues reported that in certain diabetic eyes a taut and thickened posterior hyaloid exerted macular traction that was responsible for DME. The DME in these patients did not respond to conventional macular laser photocoagulation. A PPV with stripping of the posterior hyaloid allowed the resolution of the DME with a concomitant improvement of visual acuity in these eyes. Several studies confirmed Lewis et al initial observations. Pendergast and colleagues reported on the outcomes of a retrospective case series of 55 eyes with diffuse DME and a taut premacular posterior hyaloid that underwent PPV and posterior hyaloid separation. The mean post-operative visual acuity improved from 20/160 at baseline to 20/80. About half of the eyes in this series attained an improvement of at least 2 lines of visual acuity; and 82% of eyes had a complete resolution of DME at a mean of 4.5 months. Upon the introduction of the OCT into clinical practice, Kaiser and co-workers confirmed the presence of vitreomacular traction in these eyes. Furthermore, many of these eyes had a foveal detachment caused by the vitreomacular traction.

In addition to the posterior hyaloid, the internal limiting membrane (ILM) has been suggested to cause tangential traction. Histological examination of the ILM in diabetics has shown it to be much thicker than in non-diabetic eyes.

In cases where there are no tractional elements present, PPV increases the oxygen concentration of the vitreous cavity. In the normal non-vitrectomized rabbit eye, an oxygen gradient exists within the vitreous cavity. Vitrectomy significantly increases the intravitreal oxygen concentration and eliminates the intravitreal oxygen gradient normally found in non-vitrectomized eyes. The highest concentration of oxygen is found near the retinal surface whereas the lowest concentration of oxygen is located in the anterior vitreous just posterior to the center.
References


