Intravitreal Injection of Bevacizumab in Diabetic Macular Edema: a Literature Review

Meidiana Devira Aristanti[a], Nurwasis[b]

meidianadevira@gmail.com
[a]Medical doctor, Faculty of Medicine, Universitas Airlangga, Surabaya, 60132, Indonesia
[b]Ophthalmologist (Consultant), Ophthalmology Department, Faculty of Medicine, Universitas Airlangga, Surabaya, 60132, Indonesia

Abstract

A typical sign of diabetic retinopathy is diabetic macular edema (DME), which is brought on by intraretinal fluid buildup, especially in the inner and outer plexiform layers, and is also brought on by the breakdown of the blood-retinal barrier (BRB). DME is currently one of the main causes of blindness in people of working age and its prevalence is rising globally. One of the treatments for DME is intravitreal injections of the anti-VEGF drug bevacizumab. In diffuse macular edema that is refractory to photocoagulation, intravitreal triamcinolone, or vitrectomy, the recombinant monoclonal antibody bevacizumab lowers retinal thickness and also enhances visual acuity by neutralizing the bioactivity of VEGF.

Keywords : Diabetic Macular Edema; Retinopathy Diabetic; Intravitreal Injection; Anti-VEGF, Bevacizumab

1. Introduction

Diabetic macular edema/DME thickens the retina by accumulating intraretinal fluid, notably in the inner and outer plexiform layers, which damages the blood-retinal barrier (BRB). DME is the most prevalent kind of diabetic retinopathy and the primary cause of vision loss in diabetic patients. DME can happen at different phases of diabetic retinopathy, however it usually happens at the most severe ones.

Diabetic macular edema (DME) is the most frequent cause of blindness in adults who are working age, which is on the rise globally (Schmidt-Erfurth et al., 2017) The increased prevalence of diabetes globally is to blame for this trend. In the nine years following the commencement of their diabetes, 27% of type 1 diabetics were found to have retinal edema, according to the Diabetes Control and Complications Trial (DCCT). In a different WESDR trial, macular edema occurred in 25.4% of type 2 diabetes patients who required insulin compared to 13.9% of those who did not. After 15 years of diabetes, only 50% of type 1 diabetics and 10% of type 2 diabetics develop proliferative diabetic retinopathy (PDR) (AAO, 2017).

2. Pathogenesis of Diabetic Macular Edema

Fluid accumulation in the retina as a result of blood-retinal barrier (BRB) breakdown causes DME. The fluid and electrolyte balance in the retina is tightly regulated by the blood-retinal barrier (BRB), can be compromised by diabetes-related intercellular junctional disruption, pericyte loss, and basement membrane thickening. Disruption of this barrier causes fluid to build up in the layers of the retina, just as it does with DME. Despite the complex and multiple etiology of DME, hyperglycemia is a significant risk factor for DR.

According to a significant prospective clinical investigation, the greatest risk factor for the etiology of DME is hyperglycemia. However, it is unclear exactly how it works to produce its effects. The hexosamine pathway,, the three primary metabolic pathways that contribute to the development of hyperglycemia-induced diabetic retinopathy are the polyol pathway and the protein kinase C (PKC) pathway. Each of these processes results in an increase in oxidative stress, inflammation, and vascular dysfunction. As a result of oxidative stress and inflammation, growth factors and cytokines such VEGF, angiopoietins, tumor necrosis factor (TNF), interleukins (IL), and matrix metalloproteinases (MMPs) are increased, which aids in the disruption of BRB and the formation of DME (Das et al., 2015). The development of effective treatments such laser photocoagulation, vitreoretinal surgery, and systemic and ophthalmic medicine has been facilitated by a fuller understanding of these pathways (Bahrami et al., 2016).

3. Classification of Diabetic Macular Edema

According to the American Academy of Ophthalmology, DME can be categorized into two groups: center involvement and non-center involvement, and the algorithm for pharmacological therapies in DME includes OCT-based classifications. OCT reveals macular retinal thickness if the center part of the retina is damaged. It has a diameter more than 1 mm and affects the central subfield. Diabetics typically endure eyesight loss as a result of this. In contrast, this is lacking in people who are not center involved. DME can manifest as retinal thickness with or without localized or diffuse exudate, regardless of categorization. Clinically, a ring of hard exudate may be observed as a sign of focal macular edema. significant retinal capillary anomalies with diffuse leakage as a result of significant BRB disruption are the hallmarks of diffuse macular edema. Another type of macular edema is cystoid macular edema (AAO, 2021).

The Global Diabetic Retinopathy Project Group has its own classifications for determining the severity of DME in addition to the ones mentioned above: mild, moderate, and severe DME. In mild DME, the macula's center is far from the posterior region where the edema is located. Moderate DME occurs when these structures are intact but there is edema close to the macula's center. And severe DME happens when the macula's center area is edematous (AAO, 2017).

4. Management of Diabetic Macular Edema

Basically, controlling systemic causes and managing the eyes are the management pillars for individuals with diabetic macular edema.

4.1. Control of the Systemic Factors

Strict glycemic control is advantageous in preventing and slowing the progression of diabetic retinopathy, according to all meaningful clinical trials (DCCT, UKPDS, and ACCORD). It is not advised for these patients to maintain "too tight control" with HbA1c 6% attributable to the tight control group's higher mortality and cardiovascular risk in the ACCORD trial (Frank, 2014). While the ACCORD eye research had no influence on the advancement according to the UKPDS study, lowering blood pressure lowers the risk of retinopathy or cardiovascular events prevented vision loss. The impact of systemic factor management on DME patients was not examined in the DCCT study or the UKPDS study (Chew et al., 2014). Although there is insufficient proof that systemic factor regulation plays a part in DME, it is advised that ophthalmologists and internists collaborate closely to keep blood sugar, blood pressure, and blood lipid levels under strict control (Das et al., 2015).

4.2. Spesific Ophtalmic Treatment

4.2.1. Focal / Grid Laser Photocoagulation

In comparison biological evolution, ETDRS produced better visual results employing focused or grid lasers for CSME. If the CSME maintained and the thickened, nonperfused retina or treatable abnormalities remained untreated, treatment was repeated every 4 months. Paracentral scotoma, subretinal fibrosis, and secondary choroidal neovascularization are potential side effects of focused or grid photocoagulation in DME. Treatment methods using focused and grid argon lasers have advanced with time. The DRCR net receives the majority of the modifications focused or grid photocoagulation methodology. Focal or grid lasers often give an initial 25 m macular thinning was present at the 3- to 4-month follow-up in moderate CIDME with 300- to 350-m CST. It is predicted that the focused or grid laser will increase around 10 m of macular thickness for every extra 100 m of baseline macular thickness above this threshold (Browning et al., 2018).

4.2.2. Intravitreal Injections of Corticosteroid

In ophthalmology, intravitreal injection is a crucial treatment. Ohm originally mentioned it as a remedy for retinal detachment in 1911, and research using antibiotic injections for endophthalmitis in the 1940s increased interest in this operation. There aren't many protocol-based, research-based guidelines as the risk-free administration of medications into the vitreous cavity increases in frequency. To describe the structure and composition of the vitreous and comprehend its consequences, more research is required. The highest volume of liquid that is secure injected without entering the vitreous cavity first puncturing it is generally thought to be 100 l (0.1 cc). This does not, however, take into account patient variables including age, axial length, degree of vitreous liquefaction, and phakic condition. In order to determine whether long-term intravitreal medication therapy is appropriate, the effects of frequent injections on the integrity of the sclera and trabecular meshwork should be investigated can result in problems including endophthalmitis and glaucoma (AAO, 2017).

In 2001, corticosteroids were utilized for the first time to treat diabetic macular edema (DME). Dexamethasone, fluocinolone, and triamcinolone have all been given in a variety of formulations, including solid slow-release devices, viscoelastic mixes, and particle suspensions. Dexamethasone 0.7 mg implant improved best-corrected visual acuity (BCVA) by 15 letters compared to 12.0% in 22.2% of patients of patients in the placebo group, according to a three-year randomized controlled experiment. Over a three-year period, 41.5% of phakic patients needed ocular hypotensive medication, and 59.2% of them needed cataract surgery. Although a dexamethasone intravitreal implant can effectively treat DME, anti-VEGF injections typically result in greater improvements in visual acuity (Browning et al., 2018).

4.2.3. Intravitreal Injections of Anti-VEGF

Vascular endothelial growth factor (VEGF), which has been identified as a crucial trigger for the onset of diabetic macular edema, has been connected to the condition. Normal retinal pigment epithelium cells release VEGF in response to hypoxia. VEGF levels are significantly higher in eyes with diabetic macular edema. In comparison to eyes with less macular leakage, eyes with severe macular leakage had much greater VEGF concentrations. Therefore, anti-VEGF medication can be viewed as an addition to DME therapy. (Ateeq et al ., 2014).

Aflibercept and conbercept are fusion proteins that combine the VEGF receptor with the Fc segment of immunoglobulins, whereas aptamers (pegaptanib), VEGF-specific antibodies (bevacizumab), VEGF-

specific antibody fragments (ranibizumab), and antibodies to VEGF (ranibizumab) are anti-VEGF medications. Additionally, the fusion protein binds placental growth factor and VEGF-B. On the other hand, fusion proteins and antibodies bind to all VEGF-A isoforms. Fewer injections may be necessary to treat DME due to the increased affinity of fusion proteins for VEGF (Andrade et al., 2016) (deOliveira Dias et al.,2014).

Pegaptanib was the first anti-VEGF drug used to treat DME. It selectively blocks 165 different VEGF isoforms. In 2010 and 2014, randomised controlled clinical trials demonstrating the efficacy of bevacizumab, ranibizumab, and aflibercept were conducted. A prospective randomized controlled effectiveness trial of these three drugs found no difference in efficacy after 1-2 years of follow-up in eyes with central DME and visual acuity of 20/40 or better. At one year, aflibercept outperformed ranibizumab and bevacizumab in eyes with visual acuity 20/50 or lower. After two years, Aflibercept still outperformed Bevacizumab, but not Ranibizumab (Browning et al., 2018).. On the other hand, anti-VEGF treatment of DME has the concurrent effect of improving retinopathy severity or delaying retinopathy progression. Both ranibizumab and aflibercept showed this effect (Brown et al, 2015).

Decisions on medications are influenced by both patient and physician factors. Patients should consider out-of-pocket expenses and Medigap insurance coverage. Physician-related issues include bevacizumab composition risks, industry economic motivations, and Medicare reimbursement policies (Wu et al, 2018)

4.2.4. Vitrectomy

First described in 1992 [14], vitrectomy for diabetic macular edema has since been researched as a potential first-line treatment for eyes with progressive visual acuity loss and more severe edema .(Landers e al., 2013) (Mochizuki et al., 2006). (Otani and Kishi, 2002). Refractory DME was observed to be 68% 5% in eyes with a posterior hyaloid, 5% in eyes with an epiretinal membrane, 22% in eyes with a posterior vitreous detachment, and 5% in eyes with an attached but non-taut posterior hyaloid. The effect of vitrectomy in DME is a matter of debate. According to several study teams, vitrectomy decreases macular thickness but does not enhance visual acuity..

The DRCR network conducted the biggest prospective observational study with consistent data collection. The median change in ETDRS letter score increased by 1 letter and the median change in CSMT was 97 meters during the 6-month follow-up. However, vitrectomy is also linked to edema relapse after initial recovery, partial macular hypertrophy reduction, and failure to respond to therapy. To ascertain the effectiveness of vitrectomy a prospective, multicenter, randomized clinical study is necessary for the treatment of DME. (Browning et al)..

5. Intravitreal Injection of Bevacizumab in Diabetic Macular Edema

Bevacizumab is frequently used off-label to treat DME even though it has been licensed for the treatment of by the Food and Drug Administration (FDA) advanced solid malignancies. It is a monoclonal recombinant antibody that binds to VEGF and prevents it from performing biological functions. (DRCRN, 2015) (kIMOTO ET AL., 2012).. Age-related macular degeneration (AMD) was initially treated with anti-VEGF bevacizumab intravenously, however systemic side effects have been noted. For the treatment of choroidal neovascularization (CNV) brought on by mature macular degeneration with aging, intravitreal bevacizumab infusion was originally reported in 2005 (Varma and Walia, 2013)..

Bevacizumab is frequently used to treat various ocular conditions, most of which are brought on by retinal vascular disease, including CNV brought on by proliferative diabetic retinopathy, age-related macular degeneration, and retinal vein occlusion, neovascular glaucoma, CNV brought on by pathological myopia, and retinopathy of prematurity. (Shima et al., 2008).. Even in cases of widespread macular edema

resistant to photocoagulation, intravitreal triamcinolone, or vitrectomy, bevacizumab injections into the eye have been demonstrated to enhance visual clarity and reduce retinal thickness.. (Kimoto et al ., 2012)(Arevalo2013)(Haritoglou).

For the treatment of DME, bevacizumab is more affordable than ranibizumab and aflibercept. Compared to FDA-approved ocular anti-VEGF medications, it is substantially less expensive. Anti-VEGF is reimbursed by Medicare in a variety of ways. In 2012, Medicare paid $1,903 for ranibizumab and $50 for bevacizumab. In order to treat macular degeneration, the price of a single dose of aflibercept is comparable to that of a single dose of ranibizumab, but is higher as a result of the lower dose of ranibizumab that is permitted in the US (0.3 mg). Aflibercept is about 60% less effective than ranibizumab. Ranibizumab and aflibercept have received FDA approval for intraocular usage, although bevacizumab has not.. (Browning et al., 2018). For use at high concentrations in patients with colon cancer, bevacizumab is sold in a 100 mg/4 ml preservative-free formulation. There are less systemic side effects associated with intravitreal injection than with intravenous injection since the dose used for intravenous bevacizumab delivery is roughly 1/400 of the intravenous dose and the targeted injection is intraocular rather than intravascular. (Shima et al., 2008). Magnetic resonance imaging studies revealed that microvascular permeability began to decline as soon as 24 hours following anti-VEGF injection. Usual doses ranged from 1.25 mg/0.05 ml to 2.50 mg/0.10 ml. The half-life of VEGF in the vitreous was estimated to be 4.39 days, but it was just 0.06 days in eyes that had previously undergone vitrectomies (Afaq et al., 2013) (Falayarjani and Nguyen, 2013).

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