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LITERATURE REVIEW

Intravitreal Anti-Vascular Endothelial Growth Factor (VEGF) as an Adjuvant Before Vitrectomy for Proliferative Diabetic Retinopathy (PDR)

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Abstract

Introduction: The primary treatment in proliferative diabetic retinopathy (PDR) is vitrectomy; however, direct intervention to the dense proliferative fibrovascular membrane may lead to massive hemorrhage obscuring the surgery process. **Purpose:** to review the use of anti-vascular endothelial growth factor (VEGF) as an adjuvant therapy before pars plana vitrectomy in PDR cases. **Review:** Anti-VEGF has been proposed as an adjuvant preceding the vitrectomy to lower intraoperative and post-operative complications. On the other hand, it could increase fibrosis which triggers tractional retinal detachment (TRD) in PDR cases. **Conclusion:** Intervals of five to ten days are considered the most ideal between anti-VEGF injection and pars plana vitrectomy (PPV) surgery in which the adjuvant therapy has made neovascularization regression and before the occurrence of fibrovascular contractions.

Keywords: anti-VEGF; bevacizumab; adjuvant therapy; PPV; proliferative diabetic retinopathy

Introduction

Diabetic retinopathy (DR) is the leading cause of blindness in the productive age worldwide, especially in developed countries.[1] In 2019, WHO reported an estimated world population with a DR of 146 million individuals.[2] It is estimated that one-third of people with diabetes will develop DR, and one-third will be at vision-threatening levels.[1]

Proliferative diabetic retinopathy (PDR) is the late stage of DR, characterized by neovascularisation due to diabetes-related retinal ischemia.[1],[3] This pathological new vasa is irregular, winding, and dilated, with a weak abnormal structure so that bleeding can easily occur.[4]

One of the modalities of PDR therapy with complications of vitreous bleeding and tractional retinal detachment (TRD) is pars plana vitrectomy (PPV). The proliferative tissue layers in eyes with advanced DR are multiple, thick, but brittle. This intervention in fibrovascular tissue can give rise to recurrent bleeding from various points, which may result in a challenging and time-consuming operation.

Angiogenesis is the primary pathology in PDR and vascular endothelial growth factor (VEGF) is known to have potent pro-angiogenesis activity.[5] Intravitreal anti-VEGF has been widely recommended as a preoperative adjuvant of vitrectomy to regress fibrovascular tissue and lower the incidence of intraoperative bleeding. With the reduced risk of intraoperative bleeding, the procedure and result of the vitrectomy are expected to be maximized. This hypothesis has its controversies, where some parties state that there is no significant effect on intraoperative or post-operative output. There is a risk of anti-VEGF causing TRD progression or worsening even before the vitrectomy is performed.

DR: Definition, pathogenesis, and classification

The diagnosis of DR can be established in the presence of vascular abnormalities in the retina of diabetics (Table 1). The main pathogenesis of microvascular damage is the condition of hyperglycemia in diabetics. In

Table 1. Diabetic retinopathy classification by Early Treatment Diabetic Retinopathy Study (ETDRS–the modified Airlie House classification) short version taken with modifications.

Category	Description	Management
Non-Proliferative Diabetic Retinopathy (NPDR)		
Absent Diabetic retinopathy	-	Follow-up in 12 months.
Very mild NPDR	Microaneurysm only	Mostly follow-up in 12 months.
Mild NPDR	One or more of the: • Microaneurysm • Retinal hemorrhage • Exudate • Cotton-wool spot None of significant beading or intraretinal microvascular anomaly (IRMA).	Follow-up in 6-12 months, depending on the severity of the signs, stability, systemic factors, and the patient's condition.
Moderate NPDR	• Severe retinal hemorrhage (more than standard 2A Early Treatment Diabetic Retinopathy Study (ETDRS) photography: approx. 20 medium-large per quadrant) in 1-3 quadrants or mild intraretinal microvascular abnormalities (IRMA). • Significant venous beading can exist in no more than one quadrant. • Cotton-wool spot.	• Follow-up in six months. • PDR risk up to 26% and high-risk PDR up to 8% in one year.
Severe NPDR	The 4-2-1 rule, one or more of: • Heavy hemorrhagic across four quadrants. • Significant venous beading in two or more quadrants. • Moderate IRMA in one or more quadrants.	• Follow-up In four months. • PDR risk up to 50% and high-risk PDR up to 15% in one year.
Very severe NPDR	Two or more severe NPDR criteria.	• Follow-up In four months. • Follow-up in 2-3 months. • High-risk PDR risk up to 45% in one year.
Proliferative Diabetic Retinopathy (PDR)		
Mild-moderate PDR	Neovascularization in discs (NVD) or neovascularization elsewhere (NVE) but not sufficiently meeting the criteria of high-risk PDR.	Therapeutic considerations depend on the severity of symptoms, stability, systemic factors, and the patient's condition, including adherence. If not treated, follow-up in two months.
High-risk PDR	• NVD is larger than the standard photography ETDRS 10A (approximately of the disc area). • Any NVD with vitreous bleeding. • NVE greater than ½of the area of the disc with vitreous bleeding.	
Eye diseases or advanced diabetic retinopathy	Serious vision-threatening stages: • Tractional retinal ablatio. • significant persistent vitreous bleeding. • iridis rubeosis or neovascularization of the iris (NVI) which can lead to neovascular glaucoma.	Vitrectomy pars plana (VPP) is combined with endolaser pan-retinal photocoagulation (PRP). The result of visual acuity depends on the specific indications and severity of the disease.

conditions of hyperglycemia, the initial response of blood vessels is vasa dilatation and changes in blood flow as a form of metabolic autoregulation to increased retinal metabolism in diabetics.[6]

Brownlee explained that chronic hyperglycemia can produce excess superoxide in cells and form reactive oxygen species (ROS) which will activate a pathway that increases the hexosamine pathway and polyol pathway. The resulting state of hyperglycemia also induces pericyte apoptosis, whose main function is to support the structure of the capillaries. In addition, pericyte apoptosis coupled with endothelial cell apoptosis, and thickening of the basal membrane causes damage to the blood-retinal barrier (BRB).[7],[8],[9]

Chronic mild inflammation due to endothelial and BRB damage sustained by patients is believed to initiate a leukostasis condition that leads to capillary occlusion and ischemia.[10] High exposure to glucose is associated with cell apoptosis and increased fragmentation of mitochondria and is thought to have contributed to microvascular changes.[11],[12] Clinical manifestations due to the impact of this metabolic imbalance can be found in the form of microaneurysms, and if they continue will progress to ischemic retinal blood vessels, increased vasopermeability of the retina, diabetic macular edema (DME), and neovascularization of the retina.

DR is classified by severity into two main parts, namely non-proliferative diabetic retinopathy (NPDR) and PDR. NPDR is an early phase where there are usually no significant vision complaints, but there has been a change in intraretinal vascular without the development of extraretinal fibrovascular tissue.[1],[10]

PDR is the very late stage of DR. The basic pathophysiology of PDR is angiogenesis characterized

by neovascularization due to diabetes-related retinal ischemia.[1],[3] PDR manifestations are bleeding, serum leakage, and fibrovascular tissue proliferation.

One of the vision-threatening manifestations of DR is DME, which is a thickening of the central retina due to abnormal vascular permeability caused by damage to the blood-retinal barrier.[14] DME is the most common cause of blindness in DR that can occur at any time regardless of severity. Other causes of blindness are mainly due to complications from the contraction of the proliferative fibrovascular membrane in PDR, i.e. vitreous hemorrhage and TRD.[10],[15]

PPV in PDR

Vitrectomy was first performed in cases of vitreous hemorrhage due to diabetes in 1970.[16] PPV is indicated by the presence of fractional retinal detachment complications, prolonged vitreous bleeding, and macular edema that are unresponsive to other therapies.[1],[17] Surgical techniques, in this case, include clearing vitreous turbidity due to blood, releasing retinal pull, and removing the fibrovascular membrane.

Vitreoretinal operators often encounter challenges in PDR complications. In eyes with PDR, the attachment between the fibrovascular tissue and the retina is very firm, so dissection of the neovascular membrane of the epiretinal can cause massive bleeding from various points that are difficult to overcome. The massive process of cauterization can also aggravate post-operative inflammation.[18],[19],[20],[21],[22],[23],[24]

The occurrence of intraoperative bleeding can worsen the visualization of the operating area and worsen the results of the operation both anatomically and functionally. Recurrent bleeding can also prolong the duration of surgery and significantly increase surgical complications.[25],[26] High intraocular pressure during surgery over a long period will also cause corneal edema that interferes with the visualization of surgery.[17]

When bleeding is not well controlled, blood clot cleansing, delamination, and segmentation of the epiretinal membrane not only will add tears to the retina but can also create new iatrogenic retinal damage, which increases the risk of secondary surgery for vitreous hemorrhage and repeated retinal detachment.[27]

Angiogenesis and VEGF

Angiogenesis, or the formation process of new blood vessels, is divided into two types. In the embryogenic period, vasas are formed by vasculogenesis through the process of differentiation of endothelial cells from hemangioblasts.[28],[29],[30],[31] In physiological conditions after giving birth, for example during wound healing, menstruation, pregnancy, and so on, new vases are formed by a process called neoangiogenesis, which is the angiogenesis of existing vases.[4],[28],[29],[32],[33],[34]

VEGF is a growth factor with potent proangiogenic activity.[5] VEGF also has a variety of related functions, some of which are mitogenic and anti-apoptotic against endothelial cells, increasing vascular permeability, escalating cell migration, and so on.[5]

VEGF plays an important role in pathological angiogenesis, including tumor growth, metastases, various inflammatory processes and ischemia, and macular degeneration, including DR.[5] In pathological conditions, VEGF plays a role by increasing the mobility of inflammatory cells (macrophages, granulocytes, etc.) to the site of need, maintaining local inflammatory processes and induction of proangiogenic factor synthesis by endothelial cells, platelets, smooth muscle, inflammatory cells, fibroblasts, and tumor cells.

In physiological angiogenesis, various supporting cells are involved, cell fusion occurs, and the basal membrane encloses the vasa in the final process to maintain the stability of the new vase.[4],[5] However in pathological conditions, the various cells involved (including macrophages, T-lymphocytes, platelets, and so on) trigger the release of proinflammatory cytokines.[35],[36] So that the new vasa formed is irregular, winding, dilatated, has an abnormal structure, an aberrant EC, and weakly-binding or even absent pericytes.[4]

The main trigger of angiogenesis is hypoxia, but other factors that may play a role are hypoglycemia, hypertension, low pH, mechanical stress, and chronic inflammation.[4],[37] VEGF expression has been shown to be a major factor for pathological neovascularization of the eye, and anti-VEGF therapy has been used in a variety of retinal vascular diseases involving angiogenesis.[19]

The retina of DR patients is in a state of ischemia, triggering an increase in VEGF production. VEGF is a key factor in triggering vascular permeability that causes diabetes-related macular edema and abnormal microvascular changes. As an angiogenic factor, VEGF also increases the proliferation of endothelial cells that trigger the process of neovascularization.[10]

Anti-VEGF and its role as PPV Adjuvant

In the last decade, anti-VEGF agents have become the first-line therapies for DME and PDR. Some examples of anti-VEGF agents that have been studied and used for eye diseases are pegaptanib (Macugen), ranibizumab (Lucentis), and aflibercept (EYLEA). Bevacizumab (Avastin) is also often used off-label at a more affordable price. In addition, there is also conbercept that still needs a lot of clinical research.

Indications for injection of anti-VEGF agents in DR cases are DME, retinal neovascularization regression in PDR, iridist rubeosis (neovascularization in the iris) regression, neovascular glaucoma therapy, and vitreous hemorrhage. In patients with DME intervened by intravitreal injection of ranibizumab from the beginning, severity may decrease to 2-3 levels.[38]

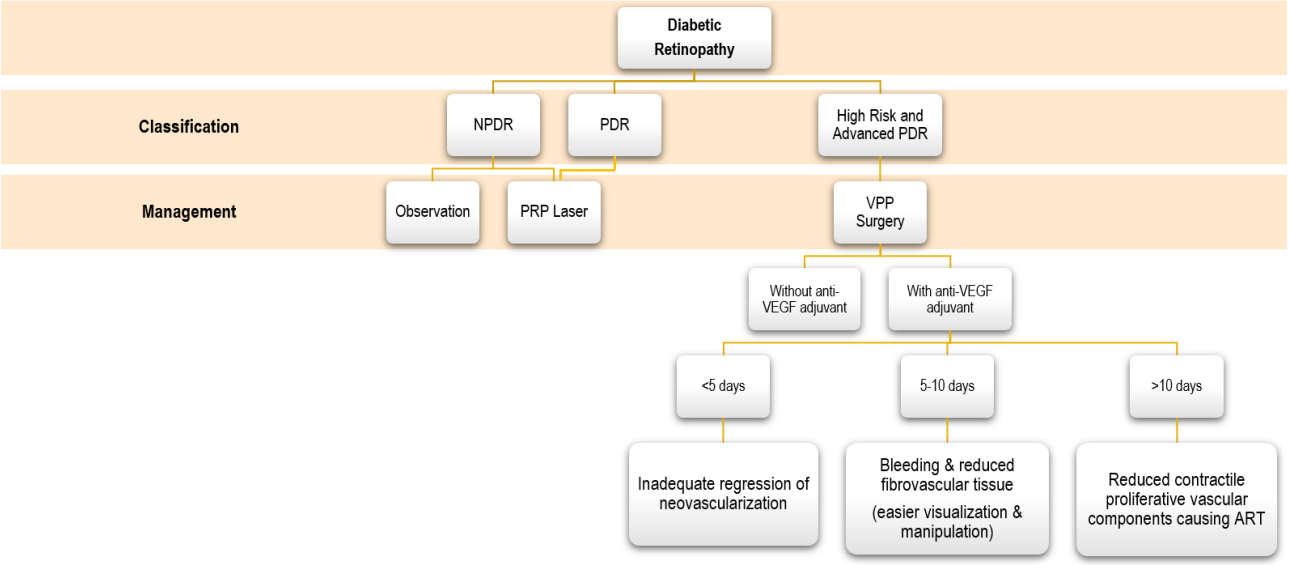

Figure 1. Classification, management, and timing of anti-VEGF adjuvants in cases of diabetic retinopathy.

The side effects of the anti-VEGF injection are mainly due to the effects of untimely contractures on the fibrovascular membrane, such as retinal tearing, TRD, or a combination of both.[1] In addition, the limitation of anti-VEGF is its relatively short half-life in vitreous so repeated therapy is required every few months, which also means a higher price, demands of a higher degree of compliance, and a higher risk of procedure-related infections.[1]

Many studies have reported the use of intravitreal anti-VEGF injections as adjuvant therapy before vitrectomy. Adjuvant therapy can be given a few days before PPV (but the start of administration in this therapy is very different from one study to another and there is no agreement yet) by injecting anti-VEGF as far as 3.5 - 4 mm from the limbus sclerocornea using the sterile technique. The goal is to reduce bleeding during surgery, minimize intraoperative complications, and facilitate delamination of the fibrovascular membrane so that the incidence of iatrogenic retinal tears is reduced and the post-operative outcome is improved.[38],[39],[40]

The main mechanism is to lower the VEGF which triggers retraction and shrinkage of the proliferative fibrovascular tissue so that the incidence of intraoperative bleeding is reduced. In one comparative study, less bleeding is reported in approximately 64% of the group of patients who received intravitreal anti-VEGF injection prior to vitrectomy than in the group that did not receive the injection.[41]

With a reduced size of fibrovascular tissue and a diminishing incidence of bleeding, intraoperative visualization will be better. The need for device replacement is low and there is an increased ease of manipulation and visualization techniques during surgery.[22],[42] Other intraoperative advantages of pre-VEGF anti-therapy are reduced surgical difficulty, duration of surgery, the incidence of iatrogenic retinal tears, frequency of silicone oil use, and the number of endodiathermic applications.[17]

Several other studies have also reported that the incidence of post-operative vitreous hemorrhage is also reduced, but it should be noted that there are two types of post-operative polycythemia vera (PV): the early-stage PV resulting from proliferative tissue dissection of re-bleeding from the same point as before surgery, the retinal area injured during surgery, and increased vascular permeability, while the advanced-stage and recurring PV is caused by leakage of new vases formed by reneovascularization.

The study of El-Sabagh et al.[43], also analyzed the components of the proliferative fibrovascular membrane in PDR patients who had received bevacizumab injection. It was obtained that the presence of collagen, CD34, and soft muscles experienced a reduction on day ten after injection, therefore from this study it was concluded that the ideal time to give a preoperative adjuvant injection was ten days earlier. It was also studied that CD34 and neovascular blood vessels were not significantly reduced until day five after injection, therefore it is concluded that before day five there is not enough time for neovascularization to regress.[43]

A meta-analysis by Zhao et al.[17] concluded that the preoperative advantage of anti-VEGF adjuvant before vitrectomy in PDR cases would facilitate surgery due to minimal bleeding, use of endodiathermy and retinal break incidences, reduced use of silicon oil and relaxing retinotomy, and shorter duration of surgery. Another advantage is that the best corrected visual acuity may be better, reducing the incidence of recurrent vitreous hemorrhage, and PV is also absorbed more quickly.[16] The blockade effect of VEGF can last up to four weeks, but all injected anti-VEGF adjuvants will also be cleared during the vitrectomy process. Post-operative recurrence of retinal detachment (RD) and PV and post-operative neovascularization requires adequate pan-retinal photocoagulation.[16],[44],[45]

On the other hand, intravitreal anti-VEGF has a proven effect of increasing fibrosis which triggers progression or even the onset of TRD after intravitreal injection of anti-VEGF in PDR cases. In a study conducted by Comyn et al, after the use of bevacizumab, a type of anti-VEGF, there was a change in the proliferative fibrovascular membrane to become fibrotic (fibrotic switch).[46],[47],[48] This hypothesis explains that molecularly anti-VEGF intravitreal triggers the formation of fibrin-fibronectin complexes, a factor for the development of fibrosis, which will increase fibrosis and worsen the progression of TRD.[49]

The incidence of progressiveness or onset of TRD after preoperative anti-VEGF can occur in up to 5.2% of all cases.[50],[51] The time interval between injection and PPV surgery is the most important predictor.[52] TRD is reported to occur when the distance between adjuvant injection and PPV is too far.[1] In another study with bevacizumab, the 5-10 day interval was compared to the 1-3 day interval assessed at the 6th-month control. The best corrected visual acuity (BCVA) is better and there are fewer post-operative complications in the interval group of 5-10 days. This can be interpreted that an interval of 1-3 days with bevacizumab may not give enough time to regress neovascularization effectively when compared to the interval of 5-10 days before PPV.[16],[53]

According to a study conducted by Wei et al.[49], the fibrin-fibronectin complex is an important factor that results in the progressiveness of fibrosis, and the level of connective tissue growth factor (CTGF) also increases and this has a high correlation with the occurrence of vitreoretinal fibrosis in PDR cases. From this study, it is stated that the formation of the fibrin-fibronectin complex is a molecule that is formed and also the cause of the occurrence of TRD after intravitreal anti-VEGF injection.[49]

In a meta-analysis with an interval of 1-20 days, only one of the 223 eyes has TRD, so it is declared relatively safe and does not initiate or increase the progression of TRD.[17] In contrast to the results of observations in 608 eyes, where an interval of fewer than six days after anti-VEGF injection is the safest time for vitrectomy, although it remains with a 10% incidence of TRD. Intervals of 6-10 days have a 12% incidence of TRD with a significantly increased risk when there is PDR-related PV. Whereas at intervals of more than ten days, the incidence of TRD exceeds half of the cases, especially in young patients.[43] Ideally, PPV is performed right after neovascularization regression and before the occurrence of fibrovascular contractions. From a molecular point of view, an interval of five to ten days is considered the most ideal time between the injection of bevacizumab and PPV surgery. If the surgery is performed before five days, the pan-endothelial sign of CD34 expressed by neovascular blood vessels has not decreased, which means that neovascularization regression is not yet adequate. After a ten days interval, the proliferation vascular component has been significantly reduced and the contractile component is also reduced so the expected effect is not optimal.[43]

The varying results in these studies may be due to differences in the research design including inclusion criteria, degree of assessment, and so on. A greater scale of research is needed with more subjects and consensus from experts so there can be a universal recommendation for the interval between the administration of intravitreal anti-VEGF adjuvant injection and the implementation of PPV.

Conclusions

The most severe manifestation of DR is PDR with the main pathology of angiogenesis. Vitrectomy in PDR with complications has a variety of intraoperative and post-operative complications that can be minimized with intravitreal anti-VEGF adjuvant therapy. Ideally, VPP is performed after enough time has passed for neovascularization regression but before the occurrence of fibrovascular contractions. From a molecular point of view, intervals of five to ten days are considered the most ideal between anti-VEGF injection and VPP surgery (Figure 1). After ten days, the proliferation vascular component has been significantly reduced and the contractile component is not much so the expected effect is not optimal. Vitrectomy can be performed after neovascularization regression and before excessive fibrovascular contractions occur to avoid progression or the onset of TRD.

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