DOI: https://doi.org/10.4038/jcosl.v30i1.93

Review article

Effect of epiretinal membranes on the efficacy of anti-VEGF agents for diabetic macular oedema: A narrative review

P. F. S. C. Fonseka[1], P. M. Hewawasam[2], D. K. T. Yomal[3], D. M. M. D. B. Dhanapala[4]

The Journal of the College of Ophthalmologists of Sri Lanka 2024; 30: 36-44

Introduction

Diabetic retinopathy is the leading cause of preventable blindness in the working age population and encompasses proliferative diabetic retinopathy (PDR) and diabetic macular oedema (DME)[80]. DME was traditionally treated with photocoagulation while anti-VEGF (Anti-Vascular Endothelial Growth Factor) agents and corticosteroids are relatively newer agents that are now well established in clinical practice[6,12]. Although these agents deliver promising results in some, a large proportion of patients respond poorly. Identification of predictors of anti-VEGF response is therefore an area of increasing clinical interest[78]. In this context evaluation of the effect of concomitant Epiretinal Membrane (ERM), on the efficacy anti-VEGF for DME is of appreciable clinical relevance[15,32,38].

Diabetes Mellitus (DM) is an endocrine disorder of global importance characterized by chronic hyperglycaemia[28]. There were 537 million people worldwide with diabetes in 2021, while 90.2 million of them were living in the South East Asian region[31]. Microvascular and macrovascular complications of diabetes are responsible for most of the morbidity and mortality associated with the disease[28]. Poor diet, sedentary lifestyle and other factors have led to a global rise in the prevalence of diabetes[91], this together with an increasingly older population has led to an increase in the incidence of diabetic macular oedema and proliferative diabetic retinopathy[80].

Diabetic macular oedema is characterised by extracellular accumulation of fluid in the retina[17] and is the leading cause of visual impairment in diabetes[12]. Tight control of blood sugar levels and hypertension is recommended to prevent the progression of DME[17]. In addition to the laser photocoagulation, corticosteroids and anti-VGEF agents a number of novel therapeutic agents have also been introduced owing to recent advancements in knowledge on the pathophysiology of the condition[80].

Epidemiology

The prevalence of DME has been revealed to be between 4.2 - 7.9% in type 1 DM and 1.4 - 12.8% in type 2 DM[44]. It affects roughly 1 out of 15 people with diabetes[13] summing up to more than 21 million sufferers worldwide[94]. DME is commoner in diabetics in the South Asian region compared to Caucasians, as is the case for diabetic retinopathy[16,19,26,73,74]. In the USA the National Health and Nutrition examination survey found that DME is twice as common as PDR[83]. A study among Sri Lankans with self reported DM found the prevalence of maculopathy to be 5.2% while prevalence of any degree of Diabetic Retinopathy (DR) in the same study was 27.4%[34]. The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) revealed the incidence of DME over 25 years to be 29%[36] while the Diabetic Control and Complications Trial (DCCT) revealed that 29% of people with Type 1 DM develop DME within 9 years[87].

Aetiology

Poor glycaemic control is a well known factor leading to the development of DME, while other systemic risk factors include but are not limited to hypertension and dyslipidaemia[18]. Chronic hyperglycaemia initiates the pathophysiological mechanisms leading to DME[5]. The DCCT found that the incidence reduces with adequate blood sugar control. Longer duration of diabetes and hypertension are also associated with DME as revealed by WESDR and DCCT trials[17,36,58,87]. There is evidence to suggest that tight BP control reduces DR development but not progression[2,51,77]. Other risk factors for the development of DME reported in literature include nephropathy, anaemia, sleep apnoea, glitazone use and pregnancy[18].

[1]*Relief House Officer, National Hospital of Sri Lanka,* [2]*Senior Registrar in Vitreo-retinal Surgery, National Eye Hospital, Colombo, Sri Lanka,* [3]*Clinical Research Assistant, National Eye Hospital, Colombo, Sri Lanka,* [4]*Consultant Vitreo-retinal Surgeon, National Eye Hospital, Colombo, Sri Lanka.*

Pathophysiology

The major pathophysiological mechanisms leading to the development of DME are inflammation and angiogenesis triggered by common stimuli, including ischaemia[14,70]. There is growing evidence that DME is a neurodegenerative disease and not merely a microvascular complication[14]. It is fair to say that the exact aetiopathogenesis of DME has not yet been elucidated[84]. The non response rate of DME to anti VEGF agents can be as high as 40% indicating the complexity of its pathophysiology[15,32,38].

VEGF (Vascular Endothelial Growth Factor) is an important cytokine glycoprotein. Its usual role is in regulating the proliferation and assembly of endothelial cells in angiogenesis. However in DR, VEGF is upregulated and assumes a pathological role[6]. Chronic hyperglycaemia seen in diabetes activates multiple metabolic pathways including the polyol pathway, protein kinase C pathway, hexasome biosynthetic pathways and leads to the accumulation of advanced glycation end products and generation of reactive oxygen species[92]. These effects and retinal ischaemia upregulate VEGF mRNA expression and increase VEGF production[6]. VEGF in turn causes phosphorylation of occludin via the protein kinase C pathway leading to disruption of the endothelial cell tight junctions[7,8]. In addition to this atypical protein kinase C activation, phosphorylation and subsequent internalization of VE cadherin, nitric oxide synthesis and release also lead to the disruption of tight junctions[6]. In addition VEGF also causes glial cell activation which produces multiple mediators many of which exert a positive feedback on VEGF secretion. VEGF also causes increased expression of adhesion molecules like ICAM - 1 on endothelial cells causing leukostasis and subsequent pro inflammatory cytokine release leading to a state of chronic inflammation and oedema in addition to causing angiogenesis[92].

Inflammation also plays a major role in the pathogenesis of DME[15,65]. Increase in blood sugar levels and other noxious stimuli can cause alterations of endothelial cells and pericytes which acts as a chemotactic stimulus, in addition expression of adhesion molecules like ICAM, VCAM and integrins lead to leukocyte adhesion and chronic inflammation as described[24,92]. Leukocyte adhesion contributes to leukostasis and capillary non perfusion leading to retinal ischaemia. The adhered leucocytes secrete cytokines and angiogenic factors causing endothelial cell tight junction disruption, increased leucocyte diapedesis, blood retinal barrier breakdown and angiogenesis. Monocytes which are so adhered will the migrate into the retina and become activated to be macrophages that secrete excess inflammatory mediators, growth factors, fibronection and leukotrienes[92]. The main inflammatory cytokines include TNF-α and IL-1β and they lead to the production of other mediators including NF-κB, IL-8, MCP-1 and IL6[46,71].

The Neurovascular Unit (NVU) also plays an important role in the pathogenesis of DME. The NVU is composed of the endothelial cells, neurons, glial cells, smooth muscles, pericytes and ECM[81]. The NVU controls blood flow and substance passage across the vessel wall. Multiple mechanisms including the activation of the innate immune system, complement system activation and retinal microglial activation lead to cellular alterations in the NVU and ultimately DME and DR[39,43,54,57,66]. Glial cells including Muller cells, astrocytes and microglia are activated due to chronic insults and secrete TNF-α, IL-1β, Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) which lead to endothelial cell damage, pericyte damage, blood retinal barrier breakdown and eventually DME[85]. The angipoetin-Tie 2 axis is another important pathway involved in DME development[35]. There is also strong evidence to suggest a role of neurodegeneration in DME and DR which underpins the potential role of neuroprotective agents in the management of DME[92].

The effect of the vitreous in the development of DME is also significant. Traction exerted on muller cells leading to muller cell hypertrophy, proliferation and vascular leakage[10,67] in addition to the tractional effect itself [3,88] on the retinal vessels and microcirculation contribute to this end. Release of certain cytokines and growth factors such as basic fibroblast growth factor may also be mediated by the effect of mechanical stresses placed on the cells[45]. The vitreous also acts as a reservoir for cytokines and growth factors that mediate DME[55,60,61]. Furthermore the vitreous reduces the oxygen delivered to the retinal surface exacerbating retinal ischaemia[62,76]. Owing to these factors TPPV (Three Port Pars Plana Vitrectomy) has a place in the management of DME specially in refractory cases where traction effects have been demonstrated[79].

ERM formation in diabetics

Epiretinal Membrane (ERM) are a relatively common retinal condition that is caused by the multiplication of fibro-cellular components at the vitreomacular interface. ERM is generally commoner in diabetics compared to the normal population. These can either be idiopathic or secondary with each type having distinct morphological forms[49,56,63].

The vitreous consists of a central body and an outer cortex which is adhered to the Internal Limiting

Membrane (ILM)[69]. As a part of normal ageing cystic spaces begin to appear within the vitreous[47,69]. The fluid within the so formed cystic spaces can leak out and accumulate in the vitreoretinal interface forming fluid filled pockets causing vitreous separation from the retina and these eventually coalesce leading to complete vitreous separation termed Posterior Vitreous Detachment PVD[56]. An anomalous PVD when present can cause traction leading to Vitreo-Retinal Interface Anomalies (VRIA) and DME[20,52,75]. This separation of the vitreous from the Vitreo-Retinal Interface (VRI) leads to ERM formation on the VRI[56]. It is the proliferation of myofibroblasts differentiated from microglial cells that have migrated to the retinal surface after partial separation of the posterior hyaloid and ILM disruption secondary to PVD that lead to ERM formation. These are usually diagnosed based on Optical Coherence Tomography (OCT)[21].

Treatment of DME

Laser photocoagulation has been established as the gold standard in the treatment of DME, however it has a non-response rate of 24.9% in diffuse DME and 12% of patients treated progress to vision loss[12]. The mechanism of action of photocoagulation is by targeting the microaneurysms which are thought to be major sites of leakage and by eliminating ischaemic areas of the retina which at as major sources of VEGF. More recently agents inhibiting the activity of VEGF have been introduced for the treatment of DME[6,12,80]. These agents are capable of binding VEGF and therefore prevent its pathological effects. A major downside of these agents is the short half life resulting in the need for multiple injections[90]. Intravitreal injection helps avoid unpleasant systemic side effects[6]. Pegatinib is the earliest form of anti VEGF agents to be introduced and binds only some isoforms of VEGF. Bevacizumab and Ranibizumab were introduced later and have the capacity to bind all isoforms. VEGF trap is a more recently developed agent which binds all isoforms with a much higher affinity[59]. However upto 40% of patients do not show adequate response to these agents reflecting the complex pathophysiology underlying the disease[15,32,38]. In addition treatment with anti VEGF agents in the presence of tractional elements can lead to what is referred to as angiofibrotic switch where the balance between angiogenic growth factors and fibrogenic growth factors is reversed leading to tractional complications[82].

Vitreomacular interface abnormalities (VMIA) have been found to reduce the efficacy of anti VEGF in DME. They are diagnosed using OCT and include ERM (an avascular membrane appearing over the ILM of the retina) and anomalous viteromacular adhesion[12]. VMIA are common in diabetes and occur in 7 - 16% of eyes with DME. These are responsible for persistent macular oedema that is non-responsive to treatment . Surgical management of VMIA using TPPV in such cases has been found to be beneficial[95]. The response of DME to TPPV depends on the OCT pattern of disease – primarily on factors such as presence/absence of traction, epiretinal membranes and PVD among others. Surgical outcomes have also been shown to depend on the surgical technique such as the removal of ILM, removal of ERM and on whether it is combined with other treatment modalities such as laser photo-coagulation, anti VEGF agents and intravitreal corticosteroids[79].

Effect of ERM on anti-VEGF response

Among those receiving anti-VEGF agents for DME 32% showed a strong response in terms of Best Corrected Visual Acuity (BCVA) and Central Retinal Thickness (CRT), 18% and 21% had a strong BCVA response but a poor CRT response and vice versa respectively. A very significant 29% of the patients had a poor BCVA and CRT response adding translating to about 50% of patients who had a poor functional (BCVA) outcome[78]. Multiple studies have evaluated possible predictors of anti-VEGF response in DME including the utility of OCT biomarkers in this regard. ERM is commoner in patients with diabetes compared to the normal population and its impact on anti-VEGF response for DME is also an area of academic and clinical interest. It is worth noting that many of the studies on this subject have excluded patients with active PDR due to the risk of angiofibrotic switch[82] and that treatment with anti-VEGF itself can induce ERM formation[11].

A prospective case series conducted by Wong and colleagues in the United Kingdom in 2016 found that the presence of vitreomacular interface disorders including ERM predicted poor BCVA and CRT outcomes over a follow up of 12 months. The study assessed 132 eyes of 96 patients and used a standardized OCT protocol for diagnosing vitreoretinal interface anomalies. All VMIA have been grouped together and no distinction had been made between ERM and other VMIAs. The presence or absence of traction has also not been considered. The study was limited due to these factors and the relatively small sample size with no control group. The use of real world data however helps make better inferences for clinical practice[86]. An interesting in-vitro study done by Namba and colleagues in Japan tried to replicate the effect of ERM in an in-vitro model to evaluate its effect on anti-VEGF response. They found that the in vitro membrane reduced the permeability for anti VEGF in a dose dependent manner thus making a case for

non-tractional effects of ERM leading to poor outcomes. This favors the elective removal of ERM irrespective of tractional components to treat DME[53]. A later study published in 2023 had evaluated the effect of multiple OCT biomarkers on anti VEGF treatment response. They found that the presence of ERM and Vitreo-Macular Traction(VMT) were negative prognostic indicators in terms of BCVA and CRT outcomes. Interestingly they had considered VMT separately from ERM. Other biomarkers considered included serous retinal detachment, diffuse retinal thickening, quantity and location of hyperreflective foci and the integrity of the Inner segment – Outer segment junction among others[29]. There were also studies that found a negative prognostic value of ERM presence after specific periods of follow up. For instance retrospective study among 119 eyes published in 2023 found that there was no significant correlation till 6 months post treatment. The total follow up duration of this study was also 12 months[48]. Interestingly Koc and colleagues evaluated the effect of ERM with and without traction separately on outcomes of DME treated with anti-VEGF. They found that while ERM with tractional components lead to a poorer outcome those without traction had no influence on outcomes[37]. The number of doses of Anti-VEGF needed to achieve clinical response has also been found to be higher in the presence of ERM in some studies[22,33]. There were multiple other studies conducted in different parts of the world that found a negative prognostic value for VMIA, but their heterogeneity in terms of duration of follow up, grouping of VMIA and other factors make them of limited use in gauging an overall picture[1,23,29,33, 41,52,89,96].

This poor response to anti VEGF agents in the presence of ERM as found in the studies mentioned above has been attributed to subclinical tractional forces on the retina, reduced diffusion of oxygen from the vitreous to retina, the ERM acting as a reservoir for VEGF, IL-6 and other inflammatory and angiogenic mediators and mechanical stretch on the retina stimulating the release of cytokines[79,93].

In contrast to the above findings, a single center retrospective study conducted in Belfast found that there was no significant correlation between the presence of VMIA including ERM on CRT or BCVA outcomes. The duration of follow up considered was 9 months. 70% of study participants with VMIA have had ERM alone while 28% have had VMT and 1% had both. Results for these different groups of VMIA have not been analyzed separately limiting the utility of this study[50]. Chang and colleagues have conducted a study among a relatively larger group of patients including 201 eyes of 142 patients that evaluated the effect of VMIA which developed during the study period on visual outcomes and found that there was no significant correlation. They had also considered all VMIA together and had a longer mean follow up duration of 40 months. They concluded that in the patients considered in their study tractional effects are probably weaker owing to the more recent development of VMIA[11].

A Turkish study conducted in 2019 found that the presence of ERM correlated with poor BCVA outcomes but had no effect on CRT improvement[22]. Multiple other studies conducted in China, Taiwan, United Kingdom and other countries have yielded similar results to the Turkish study[2,22,30,72]. There were also studies that demonstrated a significant negative correlation between ERM presence and CRT reduction outcome but not with BCVA outcome[9,27,42]. A systematic review and meta-analysis on the topic published in 2023 revealed poorer BCVA outcomes for eyes with ERM/VMT at 3 months and 12 months while there was no significant impact on CRT outcomes at the same period of follow up. This review was based on 9 clinical studies encompassing 699 eyes in total. However the studies that were included were heterogenous with varying study designs, different anti-VEGF agents, dosing regimens and different durations of follow up limiting the validity of the review results[25].

It is worth noting that many of the studies mentioned are non-randomized, retrospective in nature and have evaluated only a small proportion of patients. In addition some investigators have grouped all VMIA together in the synthesis of results. It is only a very few studies that have differentiated between ERM with and without traction in their analysis. The clinician should therefore exercise a degree of caution when interpreting these results to inform clinical practice.

Keeping these limitations in mind it is worth noting that a majority of the studies have demonstrated eyes with DME that are comorbid with ERM to respond poorly to anti-VEGF agents in terms of BCVA gains and CRT reduction. Such patients were also found to require a higher number of injections on average. Identification of possible predictors of anti-VEGF response in DME can help target anti-VEGF therapy for those who are most likely to benefit, thereby minimizing healthcare costs and avoiding unnecessary side effects. Although the current evidence is not substantial enough to cause a major shift in clinical practice, it might not be unreasonable to incorporate the role of ERM as a negative prognostic marker in patient education and counselling along with possible alternative treatment strategies. While a properly conducted systematic review and meta-analysis can serve to provide us with a better picture of the current

evidence base, large scale and well-designed clinical studies on this subject are a timely need to clear the current speculation. Research endeavors in this avenue will help generate higher levels of evidence compared to what is currently available to help guide better clinical practice.

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