Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/16064
DOI URL: http://dx.doi.org/10.21474/IJAR01/16064

RESEARCH ARTICLE

A REVIEW OF ANTI-VEGF AGENTS FOR PROLIFERATIVE DIABETIC RETINOPATHY

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Manuscript Info

Manuscript History
Received: 25 November 2022
Final Accepted: 27 December 2022
Published: January 2023

Key words:-
Diabetic Retinopathy, Diabetic Macular Edema, Proliferative Diabetic Retinopathy, Vascular Endothelial Growth Factor

Abstract

Diabetic retinopathy (DR) is commonly known among diabetic patients, which causes blindness. Proliferative diabetic retinopathy (PDR) and macular edema are the most common complications of DR that adversely impact the vision. Many observational and preclinical studies have implicated vascular endothelial growth factor (VEGF) in the pathogenesis of DR, and recent successes with anti-VEGF therapy for age-related macular degeneration (AMD) have prompted research into the application of anti-VEGF drugs to DR. Here we review the numerous early studies that suggest an important potential role for anti-VEGF agents in the management of diabetic retinopathy.

Introduction:-

Diabetic retinopathy (DR) is one of the important microvascular complication of diabetes mellitus (DM), in which chronic hyperglycemia affect the retinal microvasculature and cause critical damage leading to blindness.[1] It is estimated that, by 2030, the number of people with diabetes will exceed 500 million, making it a global threat, and among them one-third will have DR. Decreased endothelial cells, increased basal membrane thickness, permeation of the retinal blood barrier, and neovascularization are some of the impairments seen in patients with DR.[2]It has two stages based on the severity of the symptoms: non-proliferative DR (NPDR) and proliferative DR (PDR). NPDR isaccompanying with micro-aneurysm and “dot and blot” hemorrhages, whereas PDR is characterized by retinal neovascularization. PDR is also associated with retinal hemorrhage and detachment resulting in partial or complete loss of vision. Loss of central vision occurs due to increased permeability and edema of retinal vessel.[3]The suggested multifactorial underlying mechanism includes neuronal and vascular damage. The neurovascular complexes in the diabetic retina show neurochemical and electrical changes, leading to anatomical and functional impairment.[4] Vascular damage is caused by weakening of the retinal capillary wall by high glucose levels and consequent leakage of blood components into the surrounding space, leading to retinal thickening and relative ischemia, followed by proliferative growth of new vessels and macular edema.[5]

Probability of retinal complications increases with increasing duration of disease. In up to 50% of patients with type 1 diabetes and 30% of those with type 2 diabetes potentially vision-threatening retinal changes develop over time, while early retinal changes are not noticed by the patients.[6]

Vascular endothelial growth factor (VEGF) is an angiogenic factor that is expressed in a large number of retinal cells exposed to hyperglycemia. This factor increases proliferation, migration, and tubal formation. Therefore, in patients with DR, VEGF levels in the retina significantly increase, which is directly related to the progression of the

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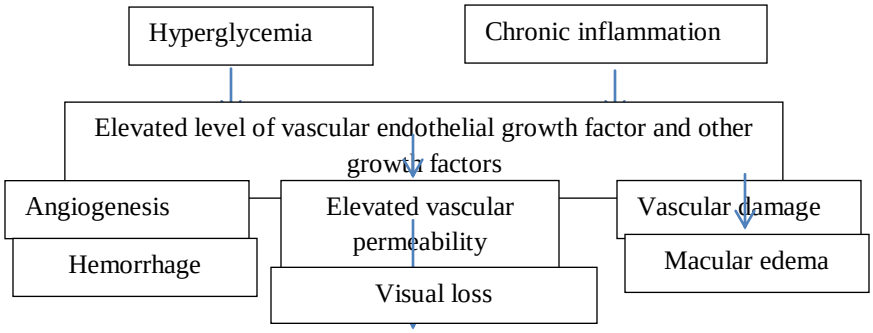
disease. VEGFantagonists can be used as a treatment to reduce angiogenesis in patients with DR. Inflammation and oxidative stress are important in the pathogenesis and development of DR.[7]



Schematic flowchart for the pathogenesis of diabetic retinopathy

Timely application and reapplication of laser photocoagulation is the mainstay of treatment to reduce visual loss and to avoid the need for vitrectomy in patients with more advanced complications of diabetic retinopathy.[8] However, despite preventive regimens and timely treatment, substantial numbers of eyes will develop complications of proliferative retinopathy and may become candidates for vitrectomy.[9] Due to the limitations of current treatment approaches, new pharmacological therapies have been developed. The novel drugs target specific biochemical pathways that cause DR through involvement of protein kinase C (PKC) activation, oxidative stress, the angiogenesis pathway, and the glycation and sorbital pathway.[10] These treatments aim to prevent diabetes-induced damage to the retinal microvasculature. In this article the role of intravitreal application of vascular endothelial growth factor (VEGF) inhibitors in will be discussed.

Role of vascular endothelial growth factor in diabetic retinopathy

Vascular endothelial growth factor (VEGF) is a powerful proangiogenic and vascular permeability factor. Several studies have demonstrated over expression of various cytokines such as VEGF, insulin-like growth factor-1 and histamine in diabetic eyes.][9]

VEGF-A has been described as a critical molecule in the pathogenesis of DR, for its role as a mediator as a vascular regulator and as neurotrophic factor and signaling regulator in the normal central nervous system.[11]Increased levels of VEGF production induceischemic retinopathies and hypoxia.[12] Induced over expression of VEGF through adeno associated virus vector results in rapid development of features of diabetic retinopathy or macular edema, depending on the targeted cell type/mode of production and diffusion of VEGF.[13]

Anti-VEGF agents

Vascular endothelial growth factor (VEGF) serves as an important therapeutic target.[8] The inhibition of VEGF effects seems to be an effective strategy to reduce retinal edema and neovascularization. Intravitreal injections of anti-VEGF drugs substantially decrease VEGF concentration in the aqueous humour and vitreous in eyes with PDR. During the past decade two anti VEGF agents have been commercialized for intravitreal use and one further drug is being widely used as an off-label treatment in DR. The potential use of other agents is presently being investigated. These agents are used as preoperative surgical adjunctive treatment.[14]

The main anti-VEGF agents with well-established efficacy in this setting are pegaptanib, bevacizumab, ranibizumab, Bevasiranib and aflibercept.[5]

Pegaptanib

The first drug developed as a selective blockade of a VEGF isoform was pegaptanib sodium. Pegaptanib acts as an anti-VEGF RNA aptamer that binds selectively to VEGF165. It was FDA approved for the treatment of choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). Intravitreal pegaptanib (IVP) may inhibit pathological neovascularization resulting from ischemic disease without affecting the physiological retinal vascularisation, what would make of it the safest anti-VEGF drug to treat patients with compromised vascularisation as is the case with diabetic patients. It has also been proposed that IVP may reverse some of the blood–retinal barrier breakdown caused by diabetes.[15]

Prospective randomized clinical trial Adamis evaluated the effects of intravitreal pegaptanib treatment on diabetic macular oedema. A retrospective analysis was also carried out to compare the effect of intravitreal pegaptanib on ocular neovascularization relative to a sham group in the same study. Of the 172 participants in the study, only 16 subjects were included in the retrospective analysis. With regard to ocular neovascularization, eight subjects (62%) in the intravitreal pegaptanib group (n = 13) showed regression of neovascularization at 36 weeks, whereas none of the eyes from sham group (n = 3) showed regression of ocular neovascularization. However, in three of the eight treated eyes (37.5%), ocular neovascularization was observed to recur at week 52 after cessation of pegaptanib at 30 weeks.[16]

Ranibizumab

One of the first reports of ranibizumab in the management of DME was by Chun et al who described a prospective, nonrandomized case series of 10 consecutive patients who received intravitreal injections of ranibizumab (0.3 mg in 5 patients or 0.5 mg in the next 5 patients) at baseline, month 1 and month 2. At 3 months, the low-dose group (0.3 mg) gained a mean of 12.0 letters and the high dose group (0.5 mg) gained 7.8 letters from baseline. There was a significant decrease in central retinal thickness in the low dose group (45.3 mm) and the high dose group (197.8 mm) at 3 months as well.[17]

Stewart et al discussed ranibizumab is superior to laser photocoagulation for the treatment of DME. Ranibizumab has thus emerged as an excellent first-line therapy for DME, either as monotherapy or in combination with laser photocoagulation of the macula. Initial intensive therapy (monthly injections) appear to produce the best short-term and long-term results.[18]

Ranibizumab for edema of the macula in diabetes (READ-1), Nguyen et al reported a prospective, nonrandomized case series of 10 patients with chronic DME who received intravitreal injections of ranibizumab (0.5 mg) at baseline and months 1, 2, 4, and 6. The mean and median improvement in visual acuity at 7 months was 12.3 and 11 letters, respectively, an improvement of approximately more than 2 lines. The visual acuity at baseline was 20/ 80 which improved to 20/40 at month 7 (P = 0.05). The mean foveal thickness decreased by 85% (from mean 503 mm to 257 mm at month 7). No adverse or systemic side effects were reported.[19]

Accordingly, Chelala et al. investigated in a prospective study the efficacy of intravitreal ranibizumab injections in PDR associated with VH. The authors graded VH into mild, moderate, and severe, and randomized patients into those treated with intravitreal injections of ranibizumab and those assigned to observation alone, who served as control group. Both groups could undergo PPV in the absence of improvement by 16 weeks or if there was any aggravation of the VH. The study showed that significantly better visual acuity measurements were recorded on all follow-up visits in the ranibizumab group.[20]

Bevacizumab

Haritoglou et al published a prospective, consecutive case series of 51 patients with chronic diffuse DME who received intravitreal bevacizumab (1.25 mg). All the patients had failed previous treatments for DME including laser photocoagulation, intravitreal injection of triamcinolone, or vitrectomy. Seventy percent of the patients received a second injection of bevacizumab. The follow-up period was between 6 and 12 weeks. The visual acuity increased by 3 lines in 29% of patients at the 6- week period and 26% of the patients at the 12-week period. The mean retinal thickness decreased from 501 mm at baseline to 416 mm at 6 weeks (P = 0.001) and 377 mm at 12 weeks (P = 0.001). Despite failing conventional therapies for DME, this study showed that improvements in visual acuity and retinal thickness could still be accomplished in the short-term with bevacizumab.[21]

Arevalo et al conducted a multicenter, retrospective study of 78 eyes of patients with DME treated with bevacizumab (1.25 mg or 2.5 mg). The average follow-up time was 6.3 months. Twenty percent of the patients required a second injection at 14 weeks and 8% required a third injection. Fifty-five percent improved greater than 2 early treatment diabetic retinopathy study lines of best-corrected visual acuity (BCVA) whereas 41% remained stable at 6 months. The mean central macular thickness at baseline was 387 mm and decreased to 275 mm at 6 months (P<0.0001). No ocular or systemic events were observed.[22]

Kubota et al. described the histology of the fibrovascular membranes in PDR treated by IVB in patient's naïve to PRP. VEGF was positively stained in the vascular endothelium but the number of positive vascular endothelial cells significantly decreased in the fibrovascular membranes treated by IVB.[23]

Aflibercept

Aflibercept is also known as VEGF Trap-Eye. It is a recombinant fusion protein comprising the key VEGFbinding domains of human VEGF receptors 1 and 2.[24] It was found to bind VEGF with a greater affinity than that of bevacizumab or ranibizumab.23 The FDA approved aflibercept as a therapy for neovascular AMD in 2011.[25]

Do et al recently reported the phase I results in 5 subjects with DME who received a single intravitreal injection of VEGF Trap (4.0 mg). Subjects were followed for 6 weeks to assess the safety and bioactivity of a single injection of VEGF Trap. After 4 weeks, the excess central foveal thickness decreased to 59 mm from 108 mm at baseline. At 6 weeks, 4 out of 5 patients showed improvement in excess foveal thickness (31% average reduction from baseline; P = 0.0625). Four of the 5 patients showed an improvement in vision with a median improvement of 3 letters at 6 weeks. No serious ocular or systemic adverse events were noted. Larger phase II studies with VEGF Trap in patients with DME are being conducted.[26]

Alagorie et al. conducted Prospective, multicenter trial study of 40 eyes with PDR and no DME treated with Aflibercept 2.0 mg monthly or quarterly 12 months. Both monthly and quarterly groups demonstrated a statistically significant regression in diabetic retinopathy severity code (DRSS) from baseline to month 12 ($p < 0.001$). The monthly group demonstrated a statistically significant greater regression of DRSS score at the month 6 visit compared with the quarterly group ($p = 0.019$). However, the difference between the two groups became statistically insignificant at month 12 ($p = 0.309$).[26]

Bevasiranib

Bevasiranib is a small interfering RNA molecule that selectively silences the mRNA encoding for VEGF. Bevasiranib was the first therapy based on the Nobel Prize-winning RNA interference (RNAi) technology to advance to Phase III clinical trials. The RNAi Assessment of Bevasiranib in DME trial was a pilot phase 2 study of the safety and preliminary efficacy of bevasiranib in patients with DME, performed on 48 patients. This pilot study showed a trend towards a decrease in macular thickness between weeks 8 and 12. The effect was more remarkable in eyes treated with higher doses.[17]

Anti-VEGF as adjunct/substitute to laser treatment for diabetic macular edema

Presently, laser photocoagulation to the macula is the standard of care to treat DME following the results of the early treatment diabetic retinopathy study. However, due to the limited results of this treatment, especially in terms of visual acuity gain in cases with diffuse DME other therapies have been attempted, either isolated or associated with laser treatment.

The results of the intravitreal application of different antiangiogenic agents in the management of DME refractory to other treatments such as laser photocoagulation, pars plana vitrectomy and intravitreal triamcinolone have been reported. These results were initially compared with those of macular laser treatment and later on with those of combined therapy (laser + intravitreal treatment).[5]

In 2005 Cunningham et al. reported on the safety and efficacy of pegaptanib injection in the treatment of DME. The patients underwent three consecutive intravitreous pegaptanib (0.3 mg, 1 mg, 3 mg) or sham injections every six weeks with additional injections and/or focal photocoagulation as needed for another 18 weeks. Median VA was better at week 36 with 0.3 mg (20/50), as compared with sham (20/63) (P = 0.04). Photocoagulation was deemed necessary in fewer subjects in each pegaptanib arm (0.3 mg vs. sham, 25% vs. 48%; P = 0.04). Subjects assigned to pegaptanib had better VA outcomes, were more likely to show reduction in central retinal thickness, and were deemed less likely to need additional therapy with photocoagulation at follow-up.[27]

Anti-VEGF as adjunct to vitrectomy

Surgery for complications of PDR is frequently necessary even in some patients who have received optimal medical care and laser treatment. It has been hypothesized that vitrectomy with ILM peeling may decrease traction on the macula, improve its oxygenation and in consequence decrease vascular permeability.[17]

Hattori et al. tested the lowest dose necessary of intravitreal bevacizumab as preoperative adjunct therapy in patients undergoing vitrectomy for PDR. They concluded that the lowest dose tested (0.16 mg) was as effective as the standard dose (1.25 mg) in reducing vitreous VEGF concentrations and also decreasing intraoperative bleeding.[28] The appropriate timing of vitrectomy after bevacizumab injection has not been well determined either, even though

most of the authors agree that a short interval (around 1 week) is preferable since tractional retinal detachments have been reported following IVB in patients with severe PDR.[29]

Huang et al. support the use of IVB in PRP naïve eyes 1 to several weeks before laser treatment in order to achieve rapid regression of vitreous haemorrhage (VH) and reduce the need for vitrectomy.[30]

Adverse effects
Some adverse effects are as follows[25]

Local side effect:
Tractional retinal detachment (TRD), FAZ enlargement, Rise in IOP, Macular hole

Other local side effects:
Endophthalmitis risk of 0.05%–1.2% per injection: level of evidence II

Systemic side effects:
The most common is hypertension, stroke, and myocardial infarctions after IVB in patient with DME.

The disadvantages of anti-VEGF agents are their shortterm effect with reperfusion of abnormal vessels in time, TRD through fibrous contraction, and the infrequent risk of endophthalmitis.60 importantly; the use of anti-VEGF agents for PDR remains off-label.[31]

Summary and Conclusions:-

In summary, there are many new promising therapeutic options being tested for DME based on inhibiting or antagonizing VEGF and itsassociated pathways. The development of ocular anti-VEGF therapy is a great breakthrough in ophthalmology. Many of these anti-VEGF treatments are in clinical trials and may be entering clinical practice in the near future. The current review has presented data to support the investigations of some of the VEGF-targeting agents in development for DME. However, the optimal dosing and schedule for these medications need to be delineated to design their proper role in the management of diabetic maculopathy. Even though diabetes mellitus and its ophthalmic complications are a large public health burden, the plethora of anti-VEGF treatments on the horizon should allow clinicians to incorporate such therapeutic agents in the armamentarium to better manage DME in the future.

For now, the existing indications for the use of antiVEGF agents in PDR include the following scenarios: (1) Before vitrectomy (not more than 1 week) due to vitreous haemorrhage. (2) Anterior segment neovascularization, preferably in those with an open angle. (3) DME with PDR

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