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ASSESSMENT OF THE EFFICACY OF VEGF DRUGS IN THE TREATMENT OF DIABETIC RETINOPATHY

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ABOUT ARTICLE

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Abstract: Aims: This study aims to compare the effectiveness of treatment between anti-vascular endothelial growth factor (anti-VEGF) agents in diabetic macular edema (DME) patients with disorganization of retinal inner layers (DRIL). Epiretinal membrane, serous macular detachment, ellipsoid zone (EZ) disorder, external limiting membrane (ELM) disorder, and hyperreflective foci were also examined.
Methods: Patients treated for DME and also had DRIL were included in the study. The study design was retrospective and cross-sectional. The complete ophthalmologic records and imaging were scanned at the beginning, 3rd-month, 6th-month, and 12th-month follow-up, and the treatments administered were recorded. Anti-VEGF agents administered to the patients were examined in three groups: bevacizumab, ranibizumab, and aflibercept.

INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of vision impairment, affecting 93 million people worldwide. Of these, 28 million have vision-threatening DR. Vision loss in DR is most commonly due to diabetic macular edema (DME) but may also be a consequence of complications of proliferative DR (PDR), such as vitreous hemorrhage from neovascularization, tractional retinal detachment, or neovascular glaucoma.

An improved understanding of the complex pathophysiology of DR has identified vascular endothelial growth factor-A (VEGF) as a key mediator of the progression to advanced disease. Development of drugs that target VEGF have revolutionized the management approach in DME and have an expanding role in the management of DR. These anti-VEGF drugs have been reported to be safe and effective through multiple clinical trials. Despite their efficacy, there are a proportion of patients who have an incomplete response to therapy. Future strategies to manage DR include alternate methods of blocking the VEGF pathway with increased efficacy and reduced number of treatments.

PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

The mechanisms resulting in the development and progression of DR are multifactorial, complex, and incompletely understood. Although primarily thought of as a microvasculopathy, there is increasing evidence to suggest neuronal and glial dysfunction are consequences of DR independent of vascular damage. Consequently, the pathogenesis of DR should consider the interactions of neuronal, glial, and vascular cells as part of a neurovascular unit affected.6

Important systemic risk factors for DR include duration of diabetes, glycemic control, type of diabetes, and hypertension. Hyperglycemia is a key component in the development of DR and is thought to lead to alteration of biochemical pathways in the retina, resulting in inflammation and oxidative stress. Cytokines such as interleukin (IL)-6, IL-1 beta, tissue necrosis factoralpha, and monocyte chemoattractant-1 are upregulated as part of this response, as are angiogenic factors such as angiopoetin-2, erythropoietin, and VEGF. These secreted factors lead to blood-retinal barrier (BRB) breakdown and increased permeability of retinal vessels resulting in DME and to neovascularization, the hallmark of PDR.

Of the cytokines and growth factors upregulated in DR, VEGF has been identified to play a critical role. There are 5 members of the VEGF family in humans: VEGF-A (commonly referred to as VEGF), VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF).

VEGF-A is a 45 kDa heparin-binding homodimeric glycoprotein and is secreted by glia, ganglion cells, endothelial cells, astrocytes, and the retinal pigment epithelium (RPE). This factor has essential physiological roles in vascular development and important roles in neuronal survival. There are 4 main isoforms of VEGF-A that bind and activate the tyrosine kinase VEGF receptor (VEGFR)-1 and VEGFR-2, which are both mainly expressed on the cell surface of the vascular endothelium. VEGFR-2 is thought to be responsible for the pathological mitogenic and microvascular permeability effects of VEGF-A. Levels of intravitreal VEGF-A are strongly correlated with advancing DR and DME.

The other members of the VEGF family have less important roles in vascular development but may play a role in DR. PlGF binds to VEGFR-1 and produces transphosphorylation of VEGFR-2, amplifying VEGF-A-driven angiogenesis and BRB breakdown through VEGFR-2. In vitro and in vivo studies support the role of PlGF in DR. Exogenous PlGF added to human RPE culture and injected into rat eyes has been shown to impair outer BRB function. PlGF knockout in an Akita mouse model of diabetes has been shown to prevent DR. Higher vitreous levels of PlGF are found with increasing levels of retinal ischemia seen in advanced DR.

There is limited evidence to suggest that VEGF-B, which also binds to VEGFR-1, is involved in the pathogenesis of DR. VEGF-B overexpression in mice via gene transfer resulted in increased choroidal and retinal neovascularization. However, levels of VEGF-B in vitreous fluid of patients with PDR are not raised compared with nondiabetic controls. It has been reported that VEGF-B prevents hyperglycemia-induced retinal apoptosis.

VEGF-C, which binds to both VEGFR-2 and VEGFR-3, has important roles in adult angiogenesis and lymphangiogenesis. VEGF-C expression is increased in diabetic retina and in vitro has been shown to potentiate the angiogenic effects of VEGF-A on VEGFR-2. Blocking VEGF-A in the retina may lead to compensatory upregulation of VEGF-C, which will in turn compensate for reduced signaling through VEGFR-2. Single nucleotide polymorphisms in the VEGF-C gene have been associated with presence of DR and DME in white patients with diabetes, further enhancing the evidence that VEGF-C may influence the development and progression of DR.

EVOLUTION OF THERAPIES FOR DIABETIC RETINOPATHY

Strategies for managing sight-threatening DR have evolved in the past 4 decades. Well-established therapies, such as laser photocoagulation and intravitreal corticosteroid therapy, may indirectly affect the VEGF pathway and signaling.

Laser Photocoagulation

Retinal photocoagulation revolutionized the management of both PDR and DME after landmark clinical trials in the 1970s and 1980s. The Diabetic Retinopathy Study (DRS) established that panretinal photocoagulation (PRP) could reduce the rates of severe vision loss in PDR by more than 50% over a period of 2 years. The destruction of photoreceptors in areas of hypoxia and subsequent reduced oxygen consumption is believed to reduce the production of VEGF driving neovascularization. Levels of intravitreal VEGF are reduced after PRP for PDR, supporting this hypothesis.

The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that focal/grid macular laser photocoagulation could reduce the rates of vision loss in clinically significant DME by half.35 Although the mechanisms of focal laser are also unclear, it is hypothesized that laser interaction with the RPE alters the expression of cytokines such as pigment epithelium derived factor (PEDF), a counterregulator of VEGF.

These laser procedures are not without associated risks and adverse effects, including loss of the peripheral visual field, pain during the procedure, severe vision loss if the fovea is targeted, and rupture of the Bruch membrane.

Corticosteroid Therapy

Corticosteroids were the initial intravitreal pharmacotherapy studied for the management of DME. These drugs inhibit the expression and action of cytokines, inhibit leukocyte recruitment, and maintain the BRB through enhancement of endothelial cell tight junctions. They may also modulate VEGF gene expression or modulate signaling downstream from the VEGFR-2.

Corticosteroids are less widely utilized for primary management of DME due to their ocular adverse effect profile, which includes raised intraocular pressure and accelerated cataract formation. However, they remain an important treatment modality for a disease that can be challenging to manage.

ANTI-VEGF DRUGS

The 3 most widely used anti-VEGF drugs are bevacizumab (Avastin, Genentech, San Francisco, CA), ranibizumab (Lucentis, Genentech, San Francisco, CA), and aflibercept (Eylea, Regeneron, Tarrytown, NY).

Pegaptanib sodium (Macugen, Eyetech Pharmaceuticals, Cedar Knolls, NJ) is an aptamer that selectively binds the VEGF-A 165 isoform and has some efficacy in the management of DME and PDR. Use of pegaptanib in DR is not widespread due to access and availability of alternate and perhaps more effective anti-VEGF agents.

Bevacizumab is a 149 kDa, full-length monoclonal antibody to all isoforms of VEGF-A. This drug was developed for its anti-angiogenic effects in neoplastic disease and proved revolutionary as an adjunct to chemotherapy in prolonging survival in metastatic cancer. It is not formulated for intravitreal use and consequently is most commonly prepared by compounding pharmacies.

RESULT

A total of 141 eyes of 100 patients were included in our study. One hundred and fifteen eyes (81.6%) had a BCVA of 0, 5, or less at the beginning. There was no statistically significant difference between the three groups regarding initial BCVA and CMT and the change in BCVA and CMT at the beginning and the 12th month ($p > 0.05$). There was a negative correlation between EZ and ELM disorders in patients and the change in BCVA at 12 months (r: 0.45 $p < 0.001$, r: 0.32 $p < 0.001$, respectively). The number of injections over five was positively correlated with the change in CMT but not with BCVA (r: - 2.35 $p = 0.005$ and r: 0.147 $p = 0.082$, respectively).

CONCLUSIONS

No statistically significant difference was found between anti-VEGF agents when treating DME patients with DRIL. In addition, we have shown that anatomically better results were obtained in those who had five or more injections, although not in terms of BCVA.

Keywords: Diabetic macular edema; Diabetic retinopathy; Disorganization of retinal inner and outer layers; Hyperreflective foci; Intravitreal injection.

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