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Antivascular Endothelial Growth Factor in Diabetic Retinopathy

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Abstract

Diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) represent the most common causes of vision loss in patients affected by diabetes mellitus. Diabetic retinopathy (DR) needs special attention because of its high public health impact and impact on quality of life of patients. Actually, laser retinal photocoagulation is the standard of care for the treatment of DR. However, laser treatment reduces the risk of moderate visual loss by approximately 50%, without a remarkable vision recovery. Thus, new approaches in the treatment of DR have been taken into account and, more specifically, the therapy employing antivascular endothelial growth factor (anti-VEGF) drugs could play a meaningful role. VEGF is a pluripotent growth factor that functions as an endothelial cell-specific mitogen and vasopermeability factor. Through these mechanisms VEGF plays a critical role in promoting angiogenesis and vascular leakage. A high level of VEGF has been detected in eyes presenting DME and PDR, and thereby VEGF is an attractive candidate as therapeutic target of pharmacological treatment in the management of DR. In the current chapter, the concepts and results of anti-VEGF therapy in the treatment of the DME and PDR are presented.

Diabetic retinopathy (DR) is considered the most frequent vascular disorder being detectable in about 40% of diabetic patients 40 years and older [1]. Today, DR is the leading cause of acquired blindness among young adults throughout the developed countries [2]. Population-based epidemiological studies have estimated that after 20 years, DR is recognized to a certain extent, and that after 30 years a proliferative DR is present in the 70% of patients with diabetes mellitus type 1 [3]. The World Health Organization estimates that about 171 million persons are affected by diabetes with an expected doubling of prevalence expected in the next 20 years [4].

Role of the Vascular Endothelial Growth Factor in Diabetic Retinopathy

Hyperglycemia is the main factor involved in the pathogenesis of DR. It results in the production of glycation end products, activation of the polyol pathway, and altered transduction of cellular signals [5–7]. The following damage to endothelial cells and pericytes, through activation of oxidative and inflammatory mechanisms, produces diabetic microangiopathy affecting small-caliber retinal vessel [8]. These alterations result in the deregulation of the mechanism of flow control with subsequently hypoxia and accumulation of fluid in the retinal tissue. Hypoxia represents the likely major inducer of vascular endothelial growth factor (VEGF) gene transcription, but the overexpression of VEGF is also upregulated in response to high glucose, protein kinase C activation, and glycation end products, all elements characterizing the impairment of glycometabolic control [5–7, 9].

VEGF is a pluripotent growth factor that functions as an endothelial cell-specific mitogen and vasopermeability factor and through these mechanisms the VEGF plays a critical role in promoting angiogenesis and vascular leakage [10–13]. In DR, the impairment of the blood retinal barrier and the increased permeability are responsible for the diabetic macular edema (DME) and several investigations underline the active role of VEGF. By disrupting the intercellular tight junctions between the retinal endothelial cells, VEGF increases the extracellular accumulation of fluid from the intravascular compartment [8]. Moreover, VEGF shows a role in mediating active intraocular neovascularization.

Elevations of VEGF levels in ocular fluids from human patients with tissue hypoxia and active neovascularization secondary to DR have been well documented [14]. The increased levels of VEGF decline when treatment with panretinal photocoagulation induces regression of neovascularization. Thus, these studies demonstrated a temporal correlation between VEGF elevations and active proliferative retinopathy evidencing the role of VEGF as a key mediator of intraocular neovascularization secondary to DR. In essence, VEGF is an attractive candidate as therapeutic target of pharmacological treatment in the management of DR.

Anti-VEGF Therapy in the Treatment of Diabetic Macular Edema and Proliferative Diabetic Retinopathy

The VEGF molecular family includes five members: placental growth factor, VEGF-A, VEGF-B, VEGF-C and VEGF-D [15]. Each of the different factors may link one or more of three VEGF receptors. Moreover, between the different factors, VEGF-A plays a major role in angiogenesis and vascular permeability. Alternative splicing of VEGF gene produces nine VEGF-A isoforms ($VEGF_{121}$, $VEGF_{145}$, $VEGF_{148}$, $VEGF_{162}$, $VEGF_{165}$, $VEGF_{165b}$, $VEGF_{183}$, $VEGF_{189}$, $VEGF_{206}$) and among them $VEGF_{165}$ is the most abundantly expressed isoform and is detected as being mainly responsible for DR.

The pathway enclosed between VEGF gene transcription and the activation of the VEGF receptor is the object of a new therapeutic approach based on the use of the VEGF antagonist. Pegaptanib, ranibizumab, bevacizumab and VEGF Trap are molecules that are able to directly bind the VEGF protein. A new and interesting therapeutic approach is the employment of bevasiranib. This molecule, interfering with messenger RNA, interrupts the synthesis of the VEGF protein. Last of all, rapamycin, employed commonly as an immunosuppressive, anti-inflammatory or antimycotic drug, reduces the activity of VEGF molecules interfering with the promoting signal, the active synthesis of VEGF, and reduces the response of endothelial cells to VEGF.

Ranibizumab

Ranibizumab is an antigen-binding fragment (F_{ab}) derived from a humanized anti-VEGF antibody and this F_{ab} inhibits all biologically active isoforms and active proteolytic fragments of VEGF-A. Currently, ranibizumab is approved by the Food and Drug Administration for the treatment of neovascular age-related macular degeneration.

Chun et al. [16] reported the first pilot study exploring the effects of two dosing regimens of ranibizumab in eyes affected by clinically significant DME. Of 10 patients enrolled, 5 received 0.3 mg ranibizumab and 5 received 0.5 mg ranibizumab at baseline and at 1 and 2 months. At month 3, 40% of patients gained more than 15 letters, 50% gained more than 10 letters, and 80% obtained an improvement of at least 1 letter in best corrected visual acuity (BCVA). At month 3, the mean decrease in central retinal thickness was 45.3 and 197.8 μm in the low- and high-dose groups, respectively. Intravitreal injections of ranibizumab were generally well tolerated and no systemic adverse events were reported.

Nguyen et al. [17] investigated the role of ranibizumab in DME in the open-label study READ-1 (Ranibizumab for Edema of the Macula in Diabetes: Phase 1). Ten patients with chronic DME received intraocular injections of 0.5 mg ranibizumab at baseline and at 1, 2, 4, and 6 months. The main outcome measures were changes in BCVA, central retinal thickness as assessed by optical coherence tomography (OCT) measurement at the 7-month examination. Mean and median values of BCVA improved at 7 months by 12.3 and 11 letters respectively. Compared to the baseline, mean foveal thickness showed a meaningful reduction decreasing from 503 to 257 μm with a 85% reduction of the excess foveal thickness present at baseline. The injections were well tolerated with no ocular or systemic adverse events.

More recently, the results of the READ-2 study were reported. READ-2 was a prospective, randomized, interventional, multicenter clinical trial designed to compare ranibizumab with focal/grid laser, alone or in combination, in DME [18]. 126 patients were randomized to receive 0.5 mg ranibizumab, focal/grid laser photocoagulation or a combination of 0.5 mg ranibizumab and focal/grid laser. Group 1, 42 patients, received 0.5 mg ranibizumab at baseline and months 1, 3, and 5. Group 2, 42 patients,

received focal/grid laser photocoagulation at baseline and month 3 if needed (center subfield thickness was >250 μm). Group 3, 42 patients, received a combination of 0.5 mg ranibizumab and focal/grid laser at baseline and month 3. The primary outcome was the change in BCVA at month 6 in comparison with baseline. At month 6, the group receiving ranibizumab alone showed a significant improvement in mean BCVA with respect to the patients receiving focal/grid laser. The group receiving combined therapy was not statistically different from groups 1 or 2. Resolutions of 50, 33, and 45% of excess foveal thickening were assessed in groups 1, 2, and 3, respectively. The RESOLVE study was specifically designed to evaluate the efficacy and safety of ranibizumab 0.5 mg in patients with visual impairment due to DME. The RESOLVE trial (a randomized, double-masked, multicenter, phase 2 study assessing the safety and efficacy of two concentrations of ranibizumab compared with non-treatment control for the treatment of DME with center involvement) evaluated the effect of ranibizumab on retinal edema and visual acuity (VA) in 151 patients with clinically significant DME. Patients with a central macular thickness of ≥300 μm were randomized to receive three monthly injections with either 0.3 or 0.5 mg ranibizumab or placebo. After the three monthly intravitreal injections, treatment was administrated on *pro re nata* basis for 9 months. The primary endpoint in the 1-year study was visual function at 6 months. The study design allowed the investigator to double the dose of ranibizumab if after 1 month the resolution of macular edema was incomplete. Moreover, retinal photocoagulation could be administered if needed.

The preliminary results were partially presented at the 2009 ARVO Meeting [19]. During the 12-month follow-up period, mean BCVA increased and mean CRT decreased continuously over time. The mean change in BCVA from baseline to the 12-month examination was –1.4 letters in the sham group. The groups receiving 0.3 and 0.5 mg gained, respectively, 11.8 and 8.8 letters. In order to provide further clarity on the effectiveness of treatments based on administration of steroidal or anti-VEGF drugs in comparison to conventional laser treatment, the DRCR net has designed a randomized, multicenter clinical trial which addressed the effects on visual acuity and on central retinal thickness in four groups receiving, respectively, intravitreal ranibizumab alone or associated with laser photocoagulation or triamcinolone associated with the laser treatment or laser treatment alone.

The study recruited 691 patients and examined a total of 854 eyes in a follow-up period of 2 years. Two hundred ninety-three eyes were randomized to received laser alone, 187 eyes were assigned to the group receiving 0.5 mg ranibizumab + prompt laser, 188 eyes received 0.5 mg ranibizumab + deferred laser (at least 24 weeks), and 186 eye were included in the group receiving 4 mg intravitreal triamcinolone + prompt laser.

At 1-year examination, the mean change in the visual acuity letter score respect to the baseline value showed a statistically significant improvement in the ranibizumab + prompt laser group (+9±11 letters) and ranibizumab + deferred laser group (+9±12) but not in the triamcinolone + prompt laser group (+4±13) compared with the laser group (+3±13).

Over the 2 years of follow-up a different correlation between visual acuity change and retinal thickness was observed in each group. A progressive reduction in mean central subfield thickness was noted in the laser group during the 24 months of follow-up; however, the mean change in visual acuity did not continue to increase from the 1- to 2-year visit as noted instead during the first year of follow-up.

In the triamcinolone + laser group, during the first year of follow-up an improvement of visual function was associated with a significant reduction in CST whereas from the 1- to 2-year examination the mean CST increased in parallel with a visual acuity reduction.

Ranibizumab groups showed a parallel visual acuity improvement associated with a CST reduction from baseline to 12-month visit and following the OCT results remained relatively stable up to 24-month examination and paralleled the visual acuity outcomes during this time.

Intraocular hypertension and cataract surgery were more frequently noted in the triamcinolone + prompt laser group in comparison to groups receiving ranibizumab + laser or laser alone.

The current large prospective randomized clinical trial confirms the preliminary promising results in the treatment of DME and suggests as a combined therapy might offer a more efficacious approach in this disorder where the multi-factorial pathogenesis involves several processes [20].

Actually, several multicenter international clinical trials (e.g. RESTORE, RIDE and RISE) are ongoing in order to evaluate the efficacy and safety of ranibizumab 0.5 mg as monotherapy or in combination with laser photocoagulation in eyes affected by DME.

With regard to the effects of ranibizumab on proliferative diabetic retinopathy (PDR), no studies are available in the literature evaluating this topic. However, DRCR.net has designed a prospective, randomized, comparative clinical trial to evaluate the role of ranibizumab or triamcinolone intravitreal injection as adjunctive treatment to panretinal photocoagulation for PDR.

Pegaptanib

Pegaptanib is a pegylated 28-nucleotide RNA aptamer that binds to the $VEGF_{164/165}$ isoform at high affinity. $VEGF_{165}$ levels are present in human eyes affected by DR with increased concentration and play an active role in promoting angiogenesis and in enhancing vascular permeability. Initially, pegaptanib was employed only in the treatment of neovascular age macular degeneration, where it obtained the approval of the Food and Drug Administration. Considering the role of $VEGF_{165}$ in DR and the safety and tolerability profile of intravitreally administered pegaptanib, a phase II trial was specifically designed to investigate the effects of pegaptanib in the management of DME.

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