**Role of Anti-VEGF in Diabetic Macular Edema**

Evangelia Papavasileiou*

*Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA, USA*

**Abstract**

Diabetic Macular Edema (DME) is the major cause of vision loss in diabetics. With introduction of anti-VEGF agents, the treatment of DME has been revolutionized, and the indication for laser therapy has been limited. This review article summarizes the current and future anti-VEGF therapies in diabetic macular edema.

**Keywords:** Diabetic macular edema; Diabetic retinopathy; Diabetes mellitus; Vascular endothelial growth factor

**Introduction**

Diabetes mellitus is the global epidemic of the 21st century. At present, there are 382 million diabetics in the world, and this number is projected to reach 592 million by the year 2035 [1]. Diabetic retinopathy, a micro-vascular complication of diabetes, is prevalent in about 35% of people with diabetes [2]. Diabetic macular edema is the major cause of visual loss in diabetics in which the breakdown of the blood-retinal barrier occurs with leakage of plasma and lipid in the macula. It is important to emphasize that diabetic maculopathy is a broader term that also includes patients with macular ischemia (often with poor prognosis) in addition to macular edema. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a large population-based study, reported the incidence of macular edema over a period of 25 years as 29% in type 1 diabetics [3]. The Diabetes Control and Complications Trial (DCCT), a landmark study showed that 27% of type 1 diabetics developed macular edema within 9 years of diabetes onset [4]. The incidence of macular edema in type 2 diabetics reported in another WESDR study was 25.4% in those who required insulin and 13.9% in those who did not require insulin [5]. Interestingly, proliferative diabetic retinopathy occurs in only 50% of type 1 diabetics after 15 years of diabetes, and in 10% of type 2 diabetics for a similar duration [6].

**Laser in DME**

Since the publication of results from the Early Treatment Diabetic Retinopathy Study (ETDRS) in 1985, focal/grid laser using small, light intensity laser burns (50-100 um in diameter) to microaneurysms, and/or diffuse area of thickening in a grid pattern has been the gold standard treatment for CSME. The procedure resulted in a 50% reduction in severe vision loss [7]. Proposed mechanisms behind this therapy include increased intraocular oxygen tension, a decreased production of vasoactive cytokines, primarily VEGF, and increased phagocytosis by Retinal Pigment Epithelial cells (RPE) and glial cells.

A recent study has shown that RPE cells at the margins of laser burns modulate various cytokines via photoreceptors [8]. With the approval of two anti-VEGF agents by the FDA in recent years, the indication of focal/grid laser is now limited to patients with non-center involving DME. A recent DRCR study examined whether prompt laser treatment strategy along with anti-VEGF therapy was better in achieving superior visual outcome than anti-VEGF therapy alone [9]. The rationale was that the prompt reduction of edema with an anti-VEGF agent would provide functional benefits from lasertreatment, and the effect might be longer lasting than that of anti-VEGF agents alone, thus reducing number of anti-VEGF injections.

However, on the contrary, the results obtained from the 3 year study have shown that focal/grid laser treatment at the initiation of intravitreal ranibizumab is not better and possibly worse for vision outcomes, than deferring laser treatment for ≥ 24 weeks in eyes with center-involving DME, although fewer injections are likely to be given when prompt laser treatment is combined with ranibizumab [10]. The study continued with this protocol for 5 years. The DRCR points out that other strategies based on individual decisions may be beneficial as the study results are based on the specific group. Some of the laser treated patients suffer from vision loss because of thermal complications like sub-retinal fibrosis or enlargement of laser scars. Selective application of subthermal intensity to RPE cells, while sparing the neuro-sensory retina, reduces these iatrogenic side effects. Longer wavelength 810 nm diode lasers reduce burn intensity and avoid absorption to macular chromophores. Also, micropulsar techniques increase the delay between pulses, and reduce the size of retinal lesions by eliminating heat diffusion and lesion growth following treatment. A pilot study of the Subthreshold Diode Micropulse (SDM) Laser showed that SDM laser photocoagulation was comparable to previous argon laser treatments in efficacy, and did not have any adverse effects or an iatrogenic retinal damage [11].

**Pharmacotherapies in DME**

Although several biochemical mechanisms for the
Role of Anti-VEGF in Diabetic Macular Edema

pathogenesis of diabetic retinopathy have been described, and the effects of drugs to block these pathways have been effective in animal models, none of these drugs has been approved by the FDA based on clinical trial results. Both aldose reductase inhibitors, Sorbinil (Pfizer) and Tolrestat (Wyeth-Ayesrt) did not show any benefit in large controlled clinical trials [12]. A large trial of aminoguanidine (inhibitors of glycation pathway) was conducted in diabetic nephropathy patients, results of which were unpublished. The failure of these trials does not rule out the role of these pathways in the pathogenesis of DR. It is likely that the drugs did not reach the retinas in effective concentrations, or the biochemical pathway targeted might not be as important in human retinopathy as it was in animal models.

Protein kinase C inhibitor

Hyperglycemia activates the enzyme, Protein Kinase C (PKC) by inducing de novo synthesis of diacylglycerol. Increased PKC β-isoform activity induces retinal vascular permeability and neovascularization in animal models. The Protein Kinase C β Inhibitor Diabetic Macular Edema Study (PKC-DMES), a multicenter, randomized, double-masked, parallel, placebo-controlled clinical trial evaluated the effect of 3 doses of orally administered Ruboxistaurin (RBX) mesylate (Eli Lilly, Indianapolis, IN), a PKC β-isoenzyme-selective inhibitor on progression of DME and the need for laser photocoagulation [13]. The delay in progression to the primary outcome (progression to sight-threatening DME or application of focal/grid photocoagulation for DME) was not statistically significant. The drug also did not prevent progression to PDR.

Anti-VEGF Therapy

VEGF is a potent vasopermeability factor. VEGF is essential in causing vascular leakage is shown in animals in which either implantation of pellets that release VEGF in the vitreous or intravitreal injection of VEGF causes breakdown of the BRB [14,15]. VEGF 164 has been shown to be a proinflammatory cytokine. In streptozotocin-induced diabetic animals, the VEGF mRNA goes up in the retina in a week by 3.2 fold, and is accompanied by increased expression of ICAM-1 and retinal vascular leakage, and injection of a VEGF receptor fusion protein can prevent all these changes. VEGF levels are significantly elevated in vitreous of patients with DME when compared with non-diabetic eye conditions [16]. There are several anti-VEGF drugs that target the molecule, VEGF. Direct inhibitors of the VEGF molecule includes the anti-VEGF aptamer, pegaptanib (Macugen®; Eyetech Pharmaceuticals, Inc. and Pfizer Inc, New York) is a ribonucleic acid aptamer that selectively targets the VEGF165 isofrom. In a phase 2/3, randomized, double-masked, 2-year trial in DME patients, intravitreal pegaptanib sodium 0.3 mg was well tolerated and demonstrated superior efficacy over the sham [17].

Ranibizumab is a monodonal antibody that blocks all isoforms of VEGF-A, and is "affinity-enhanced" to provide stronger affinity to bind to VEGF-A. This drug has been approved by the FDA for use in DME patients. Two large studies showed the benefits of intravitreal ranibizumab injections in DME patients. In the RIDE/RISE study, where patients were randomized to either two different doses of intravitreal ranibizumab (0.3 mg and 0.5 mg) or sham injection, 37-40% of patients in the ranibizumab arm showed > 15 letter improvement compared to 19% in the sham group after 3 years [18]. An interesting observation in this study was that progression of diabetic retinopathy was slowed down, and the severity of retinopathy improved in the Ranibizumab treated patients. The clinical significance of retinopathy improvement is not clear, and it is yet to be determined how long this beneficial effect of anti-VEGF therapy lasts after its cessation. The DRCR clinical trial Protocol I showed similar results and concluded that intravitreal ranibizumab with prompt or deferred laser was more effective in vision improvement through 3 years study compared with prompt laser alone for center-involving DME [19].

Bevacizumab (Avastin, Genentech) is a full-length humanized monoclonal antibody, almost three times the size of the ranibizumab molecule, which also blocks all isoforms of VEGF-A. It has been used as an “off-label” drug for the treatment of DME. Because of its much lower cost compared to other anti-VEGF drugs, it has become an affordable, popular drug in the treatment of retinal vascular diseases and ARMD. The BOLT (Bevacizumab or Laser Therapy) study compared intravitreal injections of bevacizumab (1.25 mg, 6 weekly) with focal/grid laser treatment for 2 years, and showed a visual improvement of 8.6 letters with bevacizumab injections, whereas the laser treated patients suffered visual loss of 0.5 letters [20]. The median number of treatments was 13 for bevacizumab treated patients and 4 for laser treated patients.

Afiblercept (Eylea, Regeneron) is a soluble protein that contains extracellular VEGF receptor 1 and 2 sequences fused to the Fc domain of a human IgG1 molecule, and blocks all isoforms of VEGF as well as the Placental Growth Factor (PIGF). It has approximately 100-fold greater binding affinity to VEGF-A than bevacizumab or ranibizumab. The prolonged half-life of this drug offers the advantage of every-other-month injections rather than monthly injections. In the phase 3 VIVID-DME and VISTA-DME trials, patients receiving afiblercept (2 mg monthly or every other month) had a mean vision change from baseline of 12.5 and 11.1 letters, respectively, after two years compared to a mean change from baseline in BCVA of 0.2 letters in patients receiving laser therapy [21]. The DRCR Protocol T is currently doing a head-to-head comparison of the efficacy and safety of the three anti-VEGF drugs, ranibizumab, bevacizumab and afiblercept in treatment of patients with DME [22].
Role of Anti-VEGF in Diabetic Macular Edema

a personal choice, regarding which drug to choose, and how frequently to inject after the initial three months. It is important to note that although anti-VEGF injections have become the first-line gold standard treatment in center-involving DME, there are many patients who respond poorly to anti-VEGF therapies, and the resolution of fluid is transient, and not complete [23]. Infact, in the DRCR Protocol I study, 50% of patients had persistent macular thickening even after one year of monthly injections. In these patients, the VEGF-independent pathways may be more important, and need to be targeted for the treatment of DME.

Future Strategies- Anti-VEGF Therapy

Higher dose of anti-VEGF

As there is a wide range of VEGF level in the vitreous in DME patients, it is possible that poor responders with anti-VEGF therapy may need much higher doses of anti-VEGF drugs due to higher levels of VEGF. With this rationale, a new study, READ-3 has examined the efficacy of ranibizumab at two different doses (0.5 mg and 2.0 mg) in DME patients. However, two-year results from this study showed that 0.5 mg dose was associated with a greater gain in vision compared to the 2.0 mg dose [24]. Thus higher dose (2 mg) of ranibizumab did not have additional benefit over 0.5 mg ranibizumab.

Long acting anti-VEGF delivery

Monthly intravitreal injections are a treatment burden as there are many office visits involved. Different long-acting anti-VEGF delivery systems are being investigated using bioerodible implants and microspheres, and encapsulated cells. A Phase I clinical trial using a refillable, non-biodegradable long-term drug delivery implant of ranibizumab has been completed on 20 patients with wet macular degeneration. This implant placed under the conjunctiva in the pars plana involves a 3.2 mm surgical incision without sutures, and is refilled as needed intervals in a minimally invasive office procedure. Results showed a constant, maintained improvement of visual acuity of 10 letters throughout one year [25].

VEGF DARPin

DARPins (designed ankyrin repeat proteins) are genetically engineered antibody mimetic proteins that show highly specific and high-affinity target protein binding. Newly developed anti-VEGF-A DARPin (both intravitreal and topical) based on the DARPin technology, exhibit single-digit Pico molar potency, and compared to currently approved anti-VEGF compounds, display a significantly increased potency in animal models of angiogenesis and vascular leakage. The longer half-life of DARPin allows prolonged VEGF suppression, and probably needs less frequent injections [26]. A single intraocular injection of 0.4 mg MP0112 in DME patients resulted in levels above the half-maximal inhibitory concentration and neutralization of VEGF in aqueous humor for 8-12 weeks. A double-masked phase 2 study of the DARPin (Abiciparpegol) for wet ARM D has shown that the drug provides equal or potentially higher vision gains compared to ranibizumab with fewer injections. A randomized Phase II trial (Allergan) of abicipar pegol in patients with diabetic macular edema is in progress.

Conclusions

Many of diabetic macular edema patients, who receive intravitreal anti-VEGF injections as a first line of treatment, do not show complete resolution of edema and vision improvement even after multiple injections. Focal/grid laser photocoagulation which was the gold standard treatment before, is now reserved for non-center involving DME, and may be combined with anti-VEGF therapy for a complete response. Also, other approaches like combination therapy of steroids and anti-VEGF agents, and switching to other anti-VEGF agents have been considered [22]. It is also important to note that anti-VEGF drugs have a more robust effect in the angiogenesis process (PDR or neovascularization of iris) compared to that in DME. While PDR seems to be a primarily VEGF-dependent disease, DME is a disease involving more than VEGF. So, what are the other targets beyond VEGF? More and more data is pointing towards an inflammatory disease process in DME. With multiple chemokines and cytokines known to be involved in the process, new pharmacotherapies are being developed targeting these inflammatory mediators. It is possible that in those poor responders of anti-VEGF therapy, the retina has a plethora of other inflammatory mediators that need to be targeted along with VEGF. Also, the response to anti-VEGF drug response appears so variable, and one wonders whether genetic factors play a role in determining this response to these treatments. In the future, individualized treatment based on these genetic profiles and pharmacogenetic testing, may have the potential to increase the efficacy of treatments, and reducing treatment burden for patients. Novel drug delivery systems using nanotechnology, and sustained release medications, and stem cell therapy are on the horizon. Our field of ophthalmology is currently seeing a sudden explosion of various, novel technologies and therapeutic approaches that are being developed to treat DME for visual improvement.

References


