

# Using Anti-VEGF in Diabetic Retinopathy

## Abstract

Vascular endothelium growth factor is the main pathological factor in diabetic retinopathy and diabetic macular edema (DME), Anti-VEGF agents are safe and effective in DME treatment, there are multiple Anti-VEGF agents, choosing between them is essential to individualize treatment for each patient to achieve the optimum results.

## Review Article

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**Abbreviations:** DME: Diabetic Macular Edema; DRCR: Diabetic Retinopathy Clinical Research Network; PDR: Proliferative Diabetic Retinopathy

## Introduction

In the past laser photocoagulation was the main treatment for proliferative diabetic retinopathy and diabetic macular edema as recommended by ETDRS but after 2005 Anti-VEGF has gained popularity and become the 1st line therapy for central diabetic macular edema after it was proven safe and efficacious. Anti-VEGF agents have evolved in the past 10 years from pegaptanib (macugen Bausch + Lomb) which inhibits VEGF by specifically binding to VEGF 165 isoform protein and ranibizumab (Lucentis Genentech Novartis) and bevacizumab (Avastin Genentech Roche) that inhibits VEGF A isoforms to VEGF trap fusion proteins such as aflibercept (Eylea, Regeneron Bayer), and ziv-aflibercept (Zaltrap, Regeneron Sanofi), which they inhibits VEGF A, VEGF B and PIGF where conbercept (Kanghong Biotech, Chengdu, China) which inhibits VEGF A, VEGF B, VEGF C and PIGF. Anti-VEGF agents have shifted treatment paradigms (Table 1) and prognosis which played an important role in preventing blindness, enhancing vision, and improving quality of life especially in patients in a working age that suffers from diabetes mellitus.

## Pathogenesis

The main pathogenesis of diabetic macular edema is thickened basement membrane and increased vascular permeability which increase fluid accumulation in the macula and will lead to acute inflammatory reactions and vascular dysfunction, and thus is governed by multifactorial influences which involves a lot of cytokines but in the early course of disease VEGF may play a central role [1], for that using VEGF blockade agents reduce macular edema and lead improvement of vision, where in chronic course of the disease, inflammatory cytokines may have a major role in the pathogenesis of diabetic macular edema and steroids may play a larger role. In diabetic retinopathy the metabolic and microenvironment changes cause capillary and endothelium damage which leads to a state of relative ischemia and VEGF up regulation and thus will stimulate neovascularization (i.e. proliferative retinopathy) which may lead to pre retinal, vitreous hemorrhage, and fibrovascular proliferation which interim may lead to tractional retinal detachment.

**Table 1:** A table to compare Pros and Cons of each VEGF blockade agent.

Agent	PROS	CONS
Bevacizumab	Cheap, available and effective in cases of good BCVA at the baseline	Not FDA approved, may not be effective as aflibercept in cases of worse BCVA at the baseline, inhibits only VEGF A
Ranibizumab	FDA approved, with long term proved safety and efficacy	Expansive, inhibits only VEGF A
Aflibercept	FDA approved, inhabits VEGF A, VEGF B, and PIGF, effective in cases of worse BCVA at baseline	Expansive
Ziv-aflibercept	Cheap, effective and inhabits VEGF A, VEGF B, and PIGF, but only short term safety has been established though out small group clinical trails	Not FDA approved, long term safety is unknown, needs extra steps in isolating doses when compare it preparation to bevacizumab.

## Bevacizumab

Is a monoclonal antibody which block angiogenesis by inhibiting VEGF-A, bevacizumab is FDA approved for metastatic cancer; however it gained popularity for off label intravitreal injection to treat macular diseases such as wet ARMD, macular edema secondary to retinal vein occlusion, and diabetic macular edema. Several studies have studied the safety and efficacy of bevacizumab for treating diabetic macular edema such as the BOLT study which compared intravitreal injection of bevacizumab (1.25 mg) to modified-ETDRS laser for DME patients involving the foveal center and visual acuity of 20/40 to 20/200 where participants getting bevacizumab received three injections spaced apart by 6 weeks each, followed by repeat injections every 6 weeks as needed where laser arm, received focal/grid laser photocoagulation at baseline and as often as every 4 months thereafter as needed.

At 12 months, the mean change in visual acuity was significantly better in bevacizumab arm (+5.6 letters) than in the laser arm (-4.6 letters) [2]. At 2 years, mean BCVA was 20/50 in the bevacizumab arm 20/80 in the laser arm, the bevacizumab arm gained a median of 9 ETDRS letters vs 2.5 letters for laser [3]. This study provided evidence supporting longer-term use of intravitreal bevacizumab for persistent center-involving CSME [4]. Another study Pan-American Collaborative Retina Study, which evaluated both bevacizumab 1.25 mg and 2.5 mg for diffuse diabetic maculae edema for 24 months and concluded that both doses provided stability and improvement of DME and there was no difference between 1.25 mg and 2.5 mg doses [5].

Bevacizumab was compared with dexamethasone 0.7 mg implant for DME treatment for 12 months in the BEVORDEX study which concluded that proportion of eyes that improved VA by 10 logMAR letters, is 40% in the bevacizumab arm vs 41% of the dexamethasone arm, the dexamethasone implant arm did lose 10 letters or more, in 11% of the treated eyes, mostly due to cataract, bevacizumab arm received more injections, compared to the dexamethasone arm [6].

### The rational use of Bevacizumab

Studies has proved the safety and efficacy of bevacizumab and in addition to its cheap price, bevacizumab gained global popularity for off label use for DME treatment. The best way to use bevacizumab in real life practice is for cases of central DME with good base line BCVA especially when central macular thickness is less than 400 microns. However, it is a good practice to start treating with bevacizumab despite the baseline BCVA and central macular thickness and then switch to aflibercept in case of poor response to Bevacizumab, but should take into account that switching to aflibercept may improve macular morphology with minimal visual benefits because of permanent functional damage caused by DME [7].

## Ranibizumab

Is a monoclonal antibody "FAB fragment" which block angiogenesis by inhibiting VEGF-A, which is FDA approved for intravitreal injection for DME, wet ARMD and macula edema secondary to retinal vein occlusion.

On Multiple studies have evaluated the safety and efficacy of ranibizumab for treating DME such as RESTORE study that compared intravitreal Ranibizumab vs Ranibizumab + laser vs laser therapy alone and concluded that ranibizumab combined with laser or Ranibizumab monotherapy are superior to laser therapy alone and there was no difference between Ranibizumab + laser or Ranibizumab alone [8], RESTORE Three year follow ups concluded that ranibizumab is effective in maintaining vision and central retinal thickness with no complications, however reduced number of injections required in the third year [9].

The RISE and RIDE trial is studied the efficacy and safety of ranibizumab for diabetic macular edema and were designed as double masked randomized trail comparing both monthly ranibizumab 0.3 mg, 0.5 mg and sham injection for 24 months, laser was available per protocol criteria and they concluded that ranibizumab in both doses can rapidly improve vision with low risk of both ocular and non-ocular harm [10]. After 36 months of randomization, RISE and RIDE have evaluated the maintains of efficacy without monthly injection and instead ranibizumab 0.5 mg was given as an open label to all groups as needed only based on OCT and BCVA and they concluded that vision was maintained in patients who initially received monthly injection with less frequency need of retreatment and some patients didn't need additional treatment, where sham patients who received ranibizumab didn't improve BCVA as much as the other groups who received ranibizumab at the baseline [11].

The Diabetic Retinopathy Clinical Research Network (DRCR.net) has evaluated the intravitreal ranibizumab or triamcinolone combined with focal/grid laser vs laser alone for 12 months, and they concluded that ranibizumab with prompt or deferred laser is superior to intravitreal triamcinolone with laser in phakic patients and laser alone where intravitreal triamcinolone with laser in pseudophakic patients is superior in efficacy than laser alone, and comparable with ranibizumab with prompt laser in the first 12 months [12], DRCR.net reported after 24 months follow up that ranibizumab can halt visual impairment due to central involved DME, [13]. After 36 months follow up DRCR.net reported that there is no differences between groups that received ranibizumab with prompt or deferred laser, and the number of injections was needed for treatment was six injections for the first six months, three injections in the second six months, two to three injections in the second year, and one to two injections in the third year [14]. DRCR.net concluded after 5 years follow up that eyes that received ranibizumab at the baseline had greater long-term visual improvement than those who received intravitreal triamcinolone with laser or with very deferred ranibizumab for persistent macular edema [15].

### The rational use of Ranibizumab

Ranibizumab is FDA approved for DME treatment and has been proved it long term safety and efficacy throughout multiple clinical trials. Ranibizumab can be used in real life practice for central DME especially in cases with good base line BCVA; most clinical trials suggest starting with intravitreal ranibizumab in cases of central DME may gain more vision than treatment deferral. Ranibizumab 0.3 mg is treatment of choice in patients with high risk of cerebral vascular events or cardiovascular events;

it is noteworthy to note that all anti-VEGF is not recommended in cases with history of cerebral vascular events or cardiovascular events in the last 4 months.

### Aflibercept

VEGF trap fusion protein which inhibits VEGF A, VEGF B and PlGF and gained FDA approval for intravitreal injection for DME, wet ARMD and macular edema secondary to retinal vein occlusion. Multiple clinical trials have studied the safety and efficacy of aflibercept for treating DME, such as VIVID and VISTA which they compared intravitreal aflibercept head to head with laser treatment to treat central involved diabetic macular edema, where aflibercept was administered every 4 weeks or every 8 weeks after loading doses of five intravitreal injections, they concluded the safety and efficacy of intravitreal aflibercept and its superiority over laser treatment, and they also concluded that there is no difference in the term in efficacy between administering every 4 weeks (2q4) or every 8 weeks (2q8) after loading doses of five intravitreal injections [16]. VIVID and VISTA have reported the same conclusions of superiority of intravitreal aflibercept for DME over laser treatment and no differences in efficacy between 2q4 and 2q8 groups throughout 100 weeks of follow-up [17].

### Protocol T

The Diabetic Retinopathy Clinical Research Network has studied the efficacy and safety of intravitreal aflibercept, bevacizumab, and ranibizumab for treatment of diabetic macular edema, by randomizing 660 adults with DME and within one year they concluded that aflibercept is superior in efficacy to bevacizumab and ranibizumab in treatment of diabetic macular edema in cases of baseline BCVA is 20/50 and less while all three agents are almost the same in terms of efficacy when baseline BCVA is 20/40 and better [18]. In post hoc analysis the DRCR.net concluded that in a small group of patients with good baseline BCVA with thicker macula that received bevacizumab, lead to worse visual outcome in comparison to those who received aflibercept and ranibizumab [19]. Within 2 years follow-up DRCR.net have concluded that all 3 agents have the same efficacy in cases of good BCVA at the baseline while aflibercept is superior to bevacizumab in cases of worse BCVA at the baseline but not superior to ranibizumab at 2 years follow up, as aflibercept showed superiority to ranibizumab only in the 1st year follow up in cases of worse baseline, all agents required less injections in the second year for about 5 injections while 1st year required about 9 injections [20].

### The rational use of Aflibercept

Aflibercept is FDA approved for DME treatment, its safety and efficacy has been established throughout clinical trials. Besides the high price tag, aflibercept has higher affinity and less chance of tachyphylaxis when compared to bevacizumab and ranibizumab. Aflibercept can be used in cases of central DME with worse baseline BCVA 20/50 or less. Switching to aflibercept is recommended when patient has already received multiple injections of bevacizumab or Ranibizumab with poor anatomical and visual response, however it should be noted that switching to aflibercept may improve macular morphology with minimal visual benefits because of permanent functional damage caused by DME.

### Ziv-Aflibercept

VEGF trap with the same fusion protein as aflibercept but with different high osmolar buffer solution which inhibits VEGF A, VEGF B and PlGF and gained FDA approval for metastatic cancer. Small series of clinical trials have studied the safety of intravitreal ziv-aflibercept conducted addressing the safety issue in vitro and in vivo and showed that there is non-significant RPE toxicity in vitro by Malik et al. [21] where Masnour et al. [22] has shown the safety of intravitreal Ziv aflibercept in six patients and all patients didn't show any signs of retinal ocular toxicity. However small series of studies conducted to evaluate the safety and efficacy of ziv-aflibercept for DME and showed that ziv-aflibercept is safe and effective in 12 weeks follow up by Marashi et al. [23] and for 24 weeks follow up by Andrade et al. [24].

### The rational use of Ziv-Aflibercept

Small studies have proved the short term safety and efficacy of ziv-aflibercept and in addition to its cheap price, ziv-aflibercept can be used for DME in these situations: In cases of DME with poor BCVA at the baseline, or in cases that responds poorly to bevacizumab, in countries where aflibercept is not available or cannot be afforded after proper preparation and isolation of doses which needs extra steps when compared to its preparation to bevacizumab.

### The role of ANTI-VEGF therapy in diabetic retinopathy

VEGF is upregulated as a response to relative ischemic state; many clinical trials have reported the effect of anti-VEGF on slowing the progression of diabetic retinopathy and reduction of its complications despite the anti-VEGF short-term effect. The Diabetic Retinopathy Clinical Research Network have evaluated the effect of Anti-VEGF in treatment of proliferative diabetic retinopathy (PDR) and its complications, Protocol S has evaluated the non-inferiority of visual acuity for intravitreal ranibizumab vs pan retinal photocoagulation in proliferative diabetic retinopathy and they concluded that intravitreal ranibizumab is non-inferior to pan retinal photocoagulation with less PDR complications in the ranibizumab arm, however patients presented with diabetic macular edema and proliferative retinopathy have gained more visual acuity in the Ranibizumab arm [25].

While protocol N has evaluated the role of anti-VEGF treatment in patients with vitreous hemorrhage due to proliferative diabetic retinopathy by randomizing intravitreal Ranibizumab or saline for vitreous hemorrhage, and in the 16 weeks follow up they concluded that vitrectomy rate was lower in both groups with no clinical importance between both groups, but better visual acuity, more rates of panretinal photocoagulation completion, and reduced recurrent vitreous hemorrhage in ranibizumab arm [26] which didn't persist in the 52 weeks follow up [27].

### The rational use of ANTI VEGF

Intravitreal ANTI-VEGF injection can be used to treat proliferative diabetic retinopathy in the presence of diabetic macular edema however laser can be introduced whenever proliferative diabetic retinopathy treatment failure or whenever it is hard to follow-up the patient. Intravitreal ANTI-VEGF injection can be used in the setting of vitreous hemorrhage that does not permit view for laser application, however laser should be introduced when-

ever the retinal view permits because pan laser photocoagulation is the treatment of choice in cases of vitreous hemorrhage, as Anti-VEGF have limited role because of its transit effect and recurrent hemorrhage may occur. Intravitreal ANTI-VEGF injection can be used 3 days before pars plana vitrectomy for proliferative diabetic retinopathy as it will reduce intraoperative bleeding and improve surgical outcome.

## Conclusion

Intravitreal Anti-VEGF injection is effective in the treatment of diabetic retinopathy and central macular edema, as VEGF plays a key role in the pathogenesis, there are 2 classes VEGF blockade agents, which are Anti-VEGF and VEGF trap, studies have studied the safety and efficacy of these agents and in summary all agents may be the same in terms of efficacy in good baseline BCVA where aflibercept is more effective in cases of worse baseline, BCVA all agents require less frequency rate of injections in second and third year follow up.

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