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REVIEW

A review of anti-VEGF agents for proliferative diabetic retinopathy

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Abstract

Previous research has implicated vascular endothelial growth factor (VEGF) in the pathogenesis of diabetic retinopathy (DR). Although many studies reviewed the use of anti-VEGF for diabetic macular oedema, little has been written about the use of anti-VEGF for proliferative diabetic retinopathy (PDR). This study is a review of relevant publications dealing with the use of anti-VEGF for the treatment of PDR. The articles were identified through systematic searches of PUBMED and the Cochrane Central Register of Controlled Trials. At the end of each section, we summarized the level of evidence of the scientific literature. Off-label use of anti-VEGF agents was found to be beneficial in PDR, especially in cases with neovascular glaucoma, persistent vitreous haemorrhage, and before vitrectomy. The disadvantages of the use of anti-VEGF are its short-effect duration, causing tractional retinal detachment in cases with pre-existing pre-retinal fibrosis and endophthalmitis in rare cases. There is no conclusive evidence from large randomized trials regarding the efficacy of anti-VEGF treatment in PDR. However, numerous case series, sound biochemical mechanism of action, and increasing experience with using anti-VEGF drugs can be used to support the ongoing use of this treatment modality in selected patients.
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Keywords: diabetic retinopathy; proliferative diabetic retinopathy; panretinal photocoagulation; ranibizumab; Bevacizumab; vascular endothelial growth factor

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Introduction

Proliferative diabetic retinopathy (PDR) is a major cause of blindness. Approximately, 1.5% of adults with diabetes have PDR.[1] The Diabetic Retinopathy Study showed that about half of all eyes with PDR that are left untreated will have severe vision loss (ie, visual acuity of <20/800 for at least 4 months).[2]

PDR is characterized by retinal neovascularization, serum leakage, haemorrhage, and fibrovascular proliferation in the vitreous retinal interface, which further results in vitreous haemorrhage and traction retinal detachment.[3]

The pro-angiogenic cytokine vascular endothelial growth factor (VEGF) is considered the primary factor involved in neovascularization in PDR.[4] In the base of PDR pathophysiology stands angiogenesis.[5] A key player in this process is VEGF.[6,7] Increased levels of VEGF have been reported in the vitreous humour and in fibrovascular tissues from eyes with PDR.[8–13] VEGF activates two tyrosine kinase receptors, VEGFR-1 and VEGFR-2. These receptors regulate physiological and pathological angiogenesis. VEGFR-2 is expressed mostly on vascular endothelial cells.[14] Activation of VEGFR-2 stimulates endothelial cell proliferation, migration, and survival, as well as angiogenesis and microvascular permeability as in PDR.[14]

Until recent years, panretinal photocoagulation (PRP) was the first and only choice for treating PDR. For PDR with high-risk characteristics, the Diabetic Retinopathy Study (DRS) showed a >50% decrease in the rate of severe vision loss when PRP was executed.[15] When new vessels respond to PRP by regressing within the first 3 months after treatment, the visual outcome tends to be excellent.[16] Although proven beneficial, PRP had its own complications, such as pain during treatment, loss of peripheral vision, nyctalopia, uveal effusions, worsening of macular oedema, vitreous haemorrhage and difficulty in treating eyes with vitreous haemorrhage, and advanced

cataract.[16–19] These complications brought the need for new modalities in treating PDR, such as anti-VEGF. This review will summarize the literature on anti-VEGF in treating PDR.

Antı-VEGF drugs

1. Bevacizumab (Avastin; Genentech, San Francisco, CA, USA) is a full-length recombinant humanized anti-VEGF monoclonal antibody, approved by the US Food and Drug Administration for the treatment of colorectal cancer.[20] It is a large-sized molecule (molecular weight: 148 kDa) and has twice half-life than ranibizumab.[21]

2. Ranibizumab (Lucentis; Genentech USA, Inc., San Francisco, CA, USA/Novartis Ophthalmics, Basel, Switzerland) is an engineered, humanized, recombinant antibody fragment (Fab) active against all VEGF-A isoforms. It lacks the Fc domain and has a shorter half-life than other anti-VEGF agents.[22] Lucentis is presently licensed (FDA approved) as an intravitreal agent for the treatment of wet, age-related macular degeneration (AMD).

3. Pegaptanib (Macugen, Eyetech Inc., Cedar Knolls, NJ, USA) is a 28-nucleotide RNA aptamer that binds specifically to the VEGF-A165 isomer, the major pathological VEGF protein in the eye.

4. Aflibercept (Regeneron, Tarrytown, NY, USA) with trade name Eylea (also known as VEGF Trap-Eye), is a recombinant fusion protein comprising the key VEGF-binding domains of human VEGF receptors 1 and 2. Aflibercept 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.

Materials and methods

The authors performed comprehensive searches for published studies through August 2013 that evaluated the effects of anti-VEGF agents on PDR by using electronic databases, such as PUBMED and the Cochrane Central Register of Controlled Trials. Reference lists from identified studies and key review articles dealing with the effects of anti-VEGF agents for PDR treatment were searched. The search was restricted to English-language articles. Search terms used were 'proliferative diabetic retinopathy', 'retinal neovascularization', 'vitreous

haemorrhage', 'neovascular glaucoma', 'anti-vascular endothelial growth factor', 'vascular endothelial growth factor', 'Macugen', 'pegaptanib', 'bevacizumab', 'Avastin', 'Lucentis', and 'ranibizumab' in various combinations. The authors independently identified and grouped the studies before these data were concluded. Relevant articles that were cited in the reference lists of the retrieved articles were also included. Articles considered irrelevant to PDR and duplicate studies were excluded. Levels of evidence are based on the National Health and Medical Research Council of Australia (Table 1).[24]

Anti-VEGF treatment and safety

Dosage and frequency of anti-VEGF treatment in PDR cases The optimal dose and dosing sequence for bevacizumab remains unclear. Most studies have used a dose of 1.25 mg.[25–29] Arevalo and Garcia-Amaris[30] used dosages of 1.25 mg (20.5%) and 2.5 mg (79.5%) bevacizumab, depending on the discretion of the treating clinician, and noted that the 2.5-mg dose was more effective in inducing complete regression of neovascularization relative to the 1.25-mg dose in the treatment of naive eyes.

In contrast, Avery et al[31,32] reported no significant differences between the effects of various doses of bevacizumab, ranging from 6.2 μg to 1.25 mg, on retinal neovascularization. However, they hypothesized that durability of the drug effect may vary, with higher doses producing a longer duration of effect. Hattori et al[33] showed that the lowest dose tested (0.16 mg) of intravitreal bevacizumab (IVB), as a preoperative adjunct therapy to patients before undergoing vitrectomy for PDR, was as effective as the standard dose (1.25 mg)

Table 1 National Health and Medical Research Council hierarchy of evidence-based scientific studies

Level	Intervention
I	A systematic review of level II studies
II	A randomized controlled trial
III-1	A pseudorandomized controlled trial (ie, alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomized experimental trial Cohort study Case–control study Interrupted time series with a control group
III-3	A comparative study without concurrent controls Historical control study Two or more single-arm study Interrupted time series without a parallel control group
IV	Case series with either post-test or pretest/post-test outcomes

in reducing vitreous VEGF concentrations and also decreasing intraoperative bleeding as measured by the reduced number of coagulation spots.

Arevalo *et al*[34] reported no difference in outcomes between IVB at doses of 1.25 and 2.5 mg on central macular thickness and best-corrected visual acuity (BCVA) in patients with diabetic macular oedema (DME; 41.7% with PDR).

Concerns have been raised about increasing the foveal avascular zone (FAZ) with repeated IVB injections or the use of higher-dose injections (2.5 mg),[35] although these concerns have not been proven (see below discussion). Likewise, the frequency of bevacizumab for these indications remains unclear. Most studies deferred re-injections to cases that only showed recurrence.[30]

Effectiveness of dose 1.25 mg bevacizumab at regression of neovascularization: level of evidence IV.

Rate of regression and recurrence of retinal neovascularization All anti-VEGF agents have shown promising results with regard to the regression of neo-vascularization, but they were limited by their short duration. None of the agents can substitute for the remarkable durability of PRP that qualifies it as the gold standard treatment for PDR.

The average time to recurrence of retinal neovascularization following anti-VEGF treatment ranges from 1 week[27] to 3 months.[29,31,36] Persistence of the effect of treatment 6 months post injection appears to be a standard average end point for evaluating the effectiveness of anti-VEGF treatments. Unfortunately, very few of the studies included a 6-month follow-up. In an interventional prospective case series on IVB in active PDR at the baseline examination, five eyes had iris neovascularization (NVI); 1 week after the first injection only two eyes had NVI. No cases of NVI were detected at week 6, but two cases were seen at week 12, one was a recurrence and the other was a new case.[37]

Over a 28-week period following bevacizumab treatment, Arevalo and Garcia-Amaris[30] reported that 61.4% of patients showed complete regression without fluorescein leakage, 34% of patients showed a partial regression, and 4.5% of patients showed no regression of neovascularization. Mendrinos *et al*[38] reported the complete regression of neovascularization 1 year after a single injection of pegaptanib in a patient with previous PRP.

In a retrospective analysis of 16 patients with PDR, Adamis *et al*[39] reported a possible persistent beneficial effect with intravitreal pegaptanib, with 62% of the treated eyes (*n* = 13) showing regression or a lack of neovascularization at the 6-month follow-up visit;

however, the mean number of injections was 5 (range: 3–6), and only one patient had high-risk PDR.

Minnella *et al*[40] reported that the early effects of bevacizumab were maintained at 3 months in 15 injected eyes. Likewise, Schmidinger *et al*[41] reported that 62% (8 of 13) of eyes required retreatment with bevacizumab at a 3-month follow-up visit because of the reappearance of new vessels. In another study, Mishahi *et al*[28] showed complete regression in 87.5% of Avastin-injected eyes and 25% of sham group at week 6 of follow-up ($P < 0.005$). However, at week 16, PDR recurred in a sizable number of the Avastin-treated eyes, and the complete regression rate in the two groups became identical (25%; $P = 1.000$).

In summary, these studies showed that intravitreal anti-VEGF can cause regression of neovascularization secondary to PDR. In spite of its short duration compared with PRP, even a transient effect could be of benefit in a variety of clinical settings, such as in the presence of media opacity precluding PRP, rubeosis yet to cause angle closure, or as a preoperative surgical adjuvant.

An average rate of retinal neovascularization regression of 6 weeks and recurrence at 16 weeks after one Avastin injection in PDR patient: level of evidence II.

Adverse effects
Local adverse effects of anti-VEGF
Tractional retinal detachment (TRD): In patients with severe PDR, bevacizumab can cause TRD.[42] The contraction of this fibrous tissue can cause TRD and vitreous haemorrhage.[43,44] Other presumed mechanisms include the extreme fluctuations in intraocular pressure (IOP) and deformation of the globe during intravitreal injection, resulting in vitreoretinal traction.[43,45,46] Another possible mechanism is the angio-fibrotic switch of VEGF and connective tissue growth factor (CTGF) in PDR. The anti-VEGF intravitreal injection reduces intravitreal unbound, active VEGF levels. This can cause rising CTGF levels and thus promote a switch from angiogenesis to fibrosis.[47] Arevalo *et al*[45] reported that 82% of TRD developed within 5 days of injection. The highest incidence of progression of pre-existing TRD has been reported as 18% over a 2–30-day period.[48] The only reported case of TRD after pegaptanib to date was reported after an interval of 3–5 weeks following intravitreal treatment.[49]

Risk factors for TRD following bevacizumab include a longer time interval between bevacizumab injection and vitrectomy in patients with uncontrolled diabetes, vitreous haemorrhage, and PDR resistant to PRP.[43,50] In a retrospective, multicentre, interventional, comparative case series on IVB for PDR, the risk factors for TRD after IVB were time from diagnosis of DM of >15 years, time

interval from IVB to vitrectomy of >13 days, and the use of the higher dose of IVB (2.5 mg).[51]

Risk factors for TRD after IVB in PDR patient (level of evidence III-2):

- *Time from diagnosis of DM of >15 years,*
- *Uncontrolled diabetes,*
- *Vitreous haemorrhage,*
- *PDR resistant to PRP time interval from IVB to vitrectomy of >13 days, and*
- *The use of the higher dose of IVB (2.5 mg).*

FAZ enlargement: Development of macular ischaemia following IVB has been reported in single case reports.[35,52] Lee and Koh[35] reported angiographically a FAZ enlargement following pars plana vitrectomy and treatment with 2.5 mg bevacizumab.[35]

However, macular perfusion was assessed in a prospective randomized, single-centre 2-year trial comparing 1.25 mg IVB (42 eyes) and laser therapy (38 eyes) in patients with diabetic macular edema.[53] At baseline, the mean greatest linear dimension of the FAZ in the laser group was 685 ± 262 microns and in the bevacizumab group it was 737 ± 262 microns. There was no significant difference at the 4-month time point ($P = 0.40$), with the mean greatest linear dimension of the FAZ in the laser group recorded as 678 ± 221 microns and in the bevacizumab group 678 ± 231 microns. It was concluded that at 4 months there was no evidence of worsening macular ischaemia in either group.

No evidence of development of macular ischaemia following IVB: level of evidence II.

Rise in IOP: IOP elevation following an intravitreal injection can be explained by several mechanisms. A major cause is a temporary vitreous volume increase causes an IOP spike. Studies with pegaptanib have shown such a spike normalizes within 1 h.[54] One of the other possible reasons for the raised IOP after IVB includes blockage of the trabecular meshwork by bevacizumab, which is a large 148-kDa protein.[46] The frequency of transient IOP rise after bevacizumab was reported as 0.16%.[55]

Temporary increase in IOP following IVB injection: level of evidence IV.

Macular hole: Bevacizumab can cause rapid neovascular involution with accelerated fibrosis, posterior hyaloid contraction, and macular retinal detachment. Macular hole has been reported after bevacizumab in pars plana vitrectomy in diabetic eyes although macular hole can develop during the natural course of PDR or after vitrectomy alone.[56,57]

Macular hole formation after bevacizumab in diabetic patient: level of evidence IV.

Other local side effects: Other side effects of bevacizumab include uveitis particularly at higher doses, with a reported incidence of 0.09–1.9%.[54,58]

Although VEGF has been implicated in pathological ocular neovascular disease, endogenous VEGF is very important in the maintenance and survival of retinal neurons, Muller cell, and photoreceptors of the adult retina.[59–62] This requires judicious use of long-term intravitreal anti-VEGF therapies, as they may have deleterious effects on these cells.

Other serious ocular side effects, which are general side effects from intravitreal anti-VEGF injection in general, include endophthalmitis (range in the literature 0.019–0.09%).[63] In the DRCRNe.[64] on DME patient, the rate of endophthalmitis was 0.4% per injection while in the MARINA[65] and CATT[66] trails on AMD patients the rate of endophthalmitis per injection was 0.05 and 0.7–1.2%, respectively.

Endophthalmitis risk of 0.05%–1.2% per injection: level of evidence II.

Systemic adverse effects of anti-VEGF Further studies are needed to verify the systemic side effects of anti-VEGF agents, especially in diabetic patients with significant vascular comorbidities. Among the systemic side effects, the most common is hypertension (for at least 6 weeks after the injection), followed by other cardiovascular complications.[67,68]

The largest data set for bevacizumab treatment is presently represented by a retrospective study of 1173 patients who received IVB for DME and were followed up for 12 months. A number of adverse effects were reported: 7 cases of acute elevation of blood pressure (0.4%), 6 strokes, 5 myocardial infarctions, and 5 deaths.[53] In the RISE and RIDE studies on the effect of monthly 0.5 or 0.3 mg ranibizumab or sham injection on DME patients, after 36 months of follow-up the rate of stroke was higher in the 0.5 mg group (12 (4.8%)) compared with the 0.3 mg group (5 (2.0%)) or sham/0.5 mg group (6 (2.4%)). The incidence of myocardial infarction through month 36 was 18 (7.2%) in the 0.3 mg group and 9 (3.6%) in the 0.5 mg group.[69] In the DRCRNet study, there were no difference in systemic adverse events among the three groups; however, there were 4 (4%) cardiovascular or cerebrovascular events in the sham group compared with 8 (7%) in the ranibizumab group ($P = 0.33$) and 4 (3%) in the triamcinolone group ($P = 0.86$).[64] Larger data sets exist for patients with AMD, but these are very different patient groups demographically and clinically. Increased rates of vascular events were detected in the

ranibizumab-treated patients (2.1% myocardial infarction and stroke) compared with the control group (1.1%). (Lucentis (Ranibizumab injection) Package Insert, Genentech Corporation.) The VISION trial performed in patients with neovascular AMD treated with intravitreal pegaptanib reported no systemic side effects.[70,71] The CATT Research Group compared between ranibizumab and bevacizumab for neovascular AMD, with its limited statistical power to detect important adverse events, found no significant differences between the two drugs in rates of death, arteriothrombotic events, or venous thrombotic events. However, the rate of serious systemic adverse events, primarily hospitalizations, was higher among bevacizumab-treated patients than among ranibizumab-treated patients (24.1 vs 19.0%, $P = 0.04$).[66]

In contrast, Campbell et al[72] looked retrospectively at population data and could not detect an increased risk. However, this AMD data may not be applicable in younger diabetic patients who may have significant vascular comorbidities.

It is therefore essential before starting the treatment to explain to the patients about the possible systemic side effects of intravitreal injections of anti-VEGF.

Increased risk of elevation of blood pressure, stroke, and myocardial infarctions after IVB in patient with DME: level of evidence IV.

Indications of anti-VEGF treatment for PDR

Neovascular glaucoma (NVG)   NVG in PDR occurs as a result of posterior segment ischaemia with abundant VEGF. A pilot trial on 26 eyes with NVG (73% secondary to PDR) was performed by Costagliola et al.[73] At the end of the treatment, which included three IVB injections 1 month apart, it was possible to evaluate a regression of neovascularization paralleled by an IOP ranging from 0 to 30 mm Hg (mean: 13 mm Hg). However, after 1 year of follow-up, 14 patients were treated with standard glaucoma medication, and three eyes required glaucoma valve implants. Chalam et al[74] showed complete regression of neovascularization due to aggressive NVG (69% secondary to PDR) within 3 weeks from the treatment with intracameral bevacizumab. Lim et al[75] showed a massive regression of iris neovascularization and a significant reduction in intravitreal VEGF levels in a 2-week period, and no significant changes in IOP in NVG patients treated with intracameral bevacizumab. Eid et al[76] demonstrated that combining PRP with bevacizumab ablated the ischaemic retina and ensured good success rates in patients with intractable glaucoma requiring shunt procedures. In this study, 10 eyes were injected with bevacizumab 1–2 weeks before surgery, followed by PRP; a further 10 eyes were used as control group with PRP performed only preoperatively. Over a 1-year follow-up, the mean IOP decreases were 18.8 and 15.9 mm Hg with success rates of 85 and 70% in the bevacizumab and control groups, respectively. It was postulated that the anti-VEGF treatment provided rapid regression of neovascularization and a therapeutic window of time in which to apply the more permanent thermal laser ablation of ischaemic retina.

It has been proposed that if bevacizumab is administered when the anterior chamber angle is still open, before the formation of peripheral anterior synechiae and angle closure, surgical interventions are more likely to be avoided than when it is administered at a later stage.

Regression of iris neovascularization and no significant changes in IOP in NVG patients treated with intracameral bevacizumab: level of evidence III-3.

Vitreous haemorrhage (VH)   VH is a common complication of PDR. The obscure fundus makes it difficult to monitor the course of the disease and could result in delayed management of possible retinal detachments or additional application of laser treatment. Anti-VEGF agents reduce the time required for vitreous clear-up and decrease the need for vitrectomy.[77,78] In most cases, bevacizumab was injected 1 week before the vitrectomy in order to avoid TRD in cases of severe PDR as discussed above.[37,45]

In a recent study by the Diabetic Retinopathy Clinical Research Network, the benefit of intravitreal ranibizumab was compared with intravitreal saline injections on vitrectomy rates for vitreous haemorrhage from PDR.[79] Their study on 261 participants showed a cumulative probability of vitrectomy by 16 weeks lower than expected in both groups, 12% with ranibizumab vs 17% with saline. These findings suggest little benefit to ranibizumab over saline, and there was no sham injection arm to compare. The secondary outcomes, such as better visual acuity, fewer recurrent vitreous haemorrhages, and increased chance of completing PRP, suggest at least a short-term biological effect of intravitreal ranibizumab compared with intravitreal saline. No increased risk of TRD was found.

Little benefit to ranibizumab over saline in decreasing the need for vitrectomy in PDR patient with VH: level of evidence II.

Short-term biological effect of intravitreal ranibizumab on visual acuity, fewer recurrent vitreous haemorrhages, and increased chance of completing PRP in PDR patient with VH: level of evidence II.

Intravitreal injection of anti-VEGF agents reduce the time required for vitreous clear-up: level of evidence IV.

Preoperative surgical adjunctive treatment Bevacizumab has been suggested to reduce intraoperative and postoperative bleeding when used before the vitrectomy.[43,50,80] Yeh et al[43] examined 41 eyes with severe PDR and gave half of them bevacizumab and the other half placebo 1 week before the vitrectomy. Even though intraoperative subretinal haemorrhage was more frequent in the bevacizumab group, the intraoperative bleeding was significantly worse in the placebo group. In another study, Rizzo et al[25] randomized 22 eyes with severe PDR and TRD either to IVB or to sham injection 5–7 days before vitrectomy. They showed that complication in the surgical procedure (which was evaluated by recording operative times, number of instrument exchanges, number and severity of intraoperative bleeds, dissection techniques, and intraoperative retinal tears) were reduced in the bevacizumab group. Ahmadieh et al[50] enrolled 68 eyes scheduled to undergo vitrectomy for PDR. They randomized half to IVB and half to sham injection 1 week before vitrectomy. Only 34 eyes completed the study, as patients who were treated with bevacizumab showed a significant improvement after the injection. Intraoperative bleeding, post-vitrectomy haemorrhage, and the use of intraoperative endodiathermy were significantly lower in the group treated with bevacizumab compared with the placebo group.

In the Cochrane review on anti-VEGF for prevention of postoperative vitreous cavity haemorrhage after vitrectomy (POVCH) for PDR, the results suggest that the rate of early (<3 weeks) POVCH is reduced following administration of preoperative IVB, and BCVA was improved 6 months after surgery.[81] The data was inconclusive regarding the benefit of IVB on revision vitrectomy after 6 months and density of the POVCH. Regarding adverse effect, they found a small risk of TRD and increased macular ischaemia.

In contrast to the above results, Ahn et al[82] assessed the effects of preoperative and intraoperative IVB injection on the incidence of postoperative vitreous haemorrhage after vitrectomy for PDR in 107 eyes. Cases were assigned randomly to group 1 (intravitreal 1.25 mg/0.05 ml bevacizumab injection 1–14 days before PPV), group 2 (intravitreal 1.25 mg/0.05 ml bevacizumab injection at the end of PPV), or group 3 (no IVB injection). The incidences of early (≤4 weeks) recurrent VH were 22.2, 10.8, and 32.4% in groups 1, 2, and 3, respectively ($P = 0.087$). The incidences of late (>4 weeks) recurrent VH were 11.1, 16.2, and 14.7% in groups 1, 2, and 3, respectively ($P = 0.813$). The initial time of vitreous clearing (ITVC) in groups 1, 2, and 3 were 26.4 ± 42.5, 10.3 ± 8.2, and 25.2 ± 26.1 days, respectively. The BCVA at 6 months after surgery did not differ significantly among the three groups ($P = 0.418$). In summary, the authors did

not find substantial evidence to support the adjunctive use of preoperative IVB to reduce postoperative recurrence of VH in vitrectomy for PDR.

In contrast, a meta-analysis of six randomized controlled trials (published before the study by Ahn et al[82]) and one comparative study on clinical outcomes of vitrectomy with or without IVB pre-treatment for severe diabetic retinopathy, there was a great benefit to the use of bevacizumab.[83] The surgical time was shorter in the IVB pre-treatment group ($P < 0.01$). Postoperative results showed great promise with shorter absorption of blood ($P = 0.04$), significantly less incidence of recurrent VH ($P = 0.05$), and a better final BCVA ($P = 0.003$) in the IVB group than in the control group. Complications, including final retinal detachment, and reoperation, were statistically insignificant.

In conclusion, according to the recent research, preoperative IVB has likely benefit for PDR, but randomized controlled trials with larger sample sizes and a long follow-up time are needed to better evaluate the long-term benefits and safety of bevacizumab pretreatment for severe PDR.

IVB in eyes with PDR before vitrectomy reduced surgical time, postoperative vitreous cavity haemorrhage and improved BCVA: level of evidence I.

IVB in eyes with PDR before vitrectomy reduced number of instrument exchanges, number and severity of intraoperative bleeds, dissection techniques, and intraoperative retinal tears: level of evidence II.

DME Patients with PDR in many cases have DME. Although PRP can reduce the risk of severe visual loss in patients with high-risk PDR,[17,84] a potential exists for exacerbation of macular oedema.[85–87] The ETDRS results demonstrate that, for eyes with macular oedema, focal photocoagulation is effective in reducing the risk of moderate visual loss but that scatter photocoagulation is not.[84] The Diabetic Retinopathy Clinical Network conducted a phase 3, randomized, multicentre, clinical trial with 345 eyes with a visual acuity of 20/320 or better, centre-involved DME receiving focal/grid laser, and diabetic retinopathy receiving PRP. Patients were randomly assigned to sham, 0.5 mg ranibizumab at baseline and 4 weeks, or 4 mg triamcinolone at baseline and sham at 4 weeks. Mean changes ($\pm$SD) in visual acuity letter score from baseline were significantly better in the ranibizumab ($+1 \pm 11$; $P < 0.001$) and triamcinolone ($+2 \pm 11$; $P < 0.001$) groups compared with those in the sham group (-4 ± 14) at the 14-week visit, mirroring retinal thickening results. These findings emphasize the role of ranibizumab in reducing the risk of short-term exacerbation of macular edema and associated visual acuity loss following PRP. These differences were not maintained after 56 weeks, as the

study was not designed to evaluate the effectiveness of any treatment after the 14-week study visit and only for long-term safety information. One eye (0.9%; 95% confidence interval, 0.02–4.7%) developed endophthalmitis after receiving ranibizumab.[64]

Filho et al[88] and Cho et al[89] compared PRP alone with PRP and ranibizumab or bevacizumab, respectively, for patients with high-risk PDR. In these studies, the adjunctive use of ranibizumab/bevacizumab protected against the macular swelling observed in eyes treated with PRP alone.

Ranibizumab injection before PRP treatment in patient with DME reduced the risk of short-term exacerbation of macular edema and associated visual acuity loss: level of evidence II.

Active PDR resistant to PRP   PRP is currently the standard treatment for PDR.[15] Inspite of its success in prevention and even regression in already developed NV, some NV show no regress or even progress in size,[16] many patients require additional laser treatment, and 4.5% undergo pars plana vitrectomy despite PRP.[90] Erdol et al[91] in their study of 33 eyes of 24 patients with persistent NV in PDR after PRP found that after only one intravitreal injection of 1.25 of bevacizumab complete resolution rate was 78.8% at 1 month, 63.6% at 3 months, and 45.4% at 6 months. Cintra et al[92] followed up for 1 year diabetic patients with actively leaking NV refractory to PRP who been treated with 1.5 mg of IVB. In their study of 12 patients with persistent NV, BCVA improved from 0.90 ± 0.11 at baseline to 0.70 ± 0.12 at week 48 ($P = 0.0449$). Throughout the 48-week study period, patients received a mean of 2.16 injections. Mean fluorescein leakage was $27.7 \pm 6.2 \, mm^2$ at baseline and was significantly lower at all visits post injection; at week 6, no leakage was observed ($P = 0.0001$). Moradian et al[37] evaluated the effect of bevacizumab for eyes with active progressive PDR not responsive to PRP. Bevacizumab was given to 38 eyes at baseline and after 6 or 12 weeks according to the protocol. The end point was defined as regression of active fibrovascular tissue and resolution of vitreous haemorrhage. At 6 weeks, the vitreous haemorrhage resolution was significant ($P = 0.06$), with no significant effect on fibrovascular tissue. The negative side effect, as mentioned above, was that 5.3% of eyes developed TRD.

Jorge et al[93] reported on 15 eyes with persistent, active PDR in which one injection of bevacizumab was administered. At the 12-week follow-up, fluorescein leakage was improved, with no significant adverse events. BCVA was improved significantly from baseline at all time points (1, 6, and 12 weeks), from 20/160 at baseline to approximately 20/125 at 12 weeks.

These studies show that IVB decreases leakage from diabetic neovascular lesions in persistent, active PDR. Further studies are needed, particularly on long-time side effects, in order to translate these research findings into clinical guidelines.

Bevacizumab injection induced regression of persistent NV after PRP, improves BCVA, and decreases fluorescein leakage: level of evidence III-2.

Combination treatments

Treatment combination of anti-VEGF and conventional treatment for PDR (PRP) has been reported in a few case series.[25–27,94–96]

Filho et al[88] conducted a prospective study on PRP alone compared with PRP and ranibizumab for patients with high-risk PDR. One group was treated with two sessions of PRP while in the second group intravitreal ranibizumab was administered at the end of the first laser session. Intravitreal ranibizumab after PRP showed a larger reduction in total area (mm^2) of fluorescein leakage at week 48 compared with PRP.

In a similar study, Tonello et al[95] showed no significant improvement in BCVA, but the total area of actively leaking NVs was significantly reduced in the PRP plus IVB group compared with the PRP group at weeks 4, 9, and 16 ($P < 0.001$). In this study, the bevacizumab was administered at the end of the second laser session. Cho et al[89] examined the benefit of IVB before the PRP as an adjunctive treatment. In his study on 41 eyes with high-risk PDR patient, IVB was injected 1 week before initiating PRP. BCVA showed no change in the PRP 'Plus' group, whereas in the PRP group it was significantly worse at 3 months ($P = 0.041$). There was no significant change in BCVA in both groups when CME was evident. The number of eyes that developed vitreous haemorrhage was significantly lower in the 'Plus' group than in the PRP alone group ($P = 0.023$).

In conclusion, intravitreal anti-VEGF before and with PRP has great benefit in the treatment of high-risk PDR.

Anti-VEGF at the end of PRP treatment reduced fluorescein leakage in high-risk PDR: level of evidence III-3.

Future treatment

Regarding diabetic retinopathy, there are only studies on aflibercept and DME.[97–99] There are no current studies on aflibercept and PDR.

Conclusions

The use of anti-VEGF agents in PDR is an evolving field. Although PRP is considered the first line for PDR,

anti-VEGF drugs are slowly finding their place in the management of PDR. This is true especially in those cases when there is difficulty in performing PRP (such as vitreous haemorrhage and dense cataract) or when PRP has failed in preventing PDR progression.

For now, the existing indications for the use of anti-VEGF 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.

The disadvantages of anti-VEGF agents are their short-term 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.

At present, there are no large, co-ordinated randomized trials into this area to demonstrate high-level evidence. However, the above evidence can be used as a justification to treat PDR in specific indications to improve patient's outcome on a case-by-case basis when the practitioner is vigilant of the potential adverse effects. In the near future, results of ongoing trials such as the DRCR network 'Prompt Panretinal Photocoagulation Versus Ranibizumab plus Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy (Protocol S)' will provide relevant information.[100]

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