

# Timing of neovascular regression in eyes with high-risk proliferative diabetic retinopathy without macular edema treated initially with intravitreal bevacizumab

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**Purpose:** To determine the timing of neovascular regression after intravitreal injection of bevacizumab (Avastin®) 1.25 mg given as initial therapy for eyes with high-risk proliferative diabetic retinopathy (PDR) without clinically significant macular edema (CSME).

**Patients and methods:** In this prospective uncontrolled interventional study, eyes with high-risk PDR without CSME were treated initially with intravitreal injections of bevacizumab 1.25 mg given every 4 weeks until no neovessels were detected, followed by standard panretinal photocoagulation (PRP). Patients were examined 48 hours, 1, 2, and 4 weeks after each injection to determine the status of neovascularization.

**Results:** Twenty-one patients (24 eyes) were included in the study. Forty-eight hours after the first injection of bevacizumab, we observed complete neovascular regression in 20 (83%) eyes. Neovascular regression was maintained in the same number of eyes in the first 2 weeks. At 4 weeks, three eyes displayed neovascular recurrence, and a second injection of bevacizumab was given to the seven eyes with persistent or recurrent neovascularization. Complete neovascular regression was observed in six (86%) eyes after 48 hours and was maintained for 2 weeks following the second bevacizumab injection. Two eyes required a third injection and had complete neovascular regression when assessed after 48 hours and 4 weeks.

**Conclusion:** The majority of neovessels completely regressed within 48 hours after intravitreal injection of bevacizumab given as initial therapy for high-risk PDR without CSME. The full neovascular regressive effect occurred within 48 hours and was maintained for at least 2 weeks.

**Keywords:** proliferative diabetic retinopathy, anti-vascular endothelial growth factor (anti-VEGF), bevacizumab

## Introduction

Diabetic retinopathy afflicts about 93 million people worldwide, including 17 million with proliferative diabetic retinopathy (PDR),<sup>1</sup> which is the leading cause of vision loss in diabetes.<sup>2</sup> The Diabetic Retinopathy Study recommended prompt treatment with panretinal photocoagulation (PRP) for eyes with high-risk PDR, because without treatment this group had a more than 50% risk of severe visual loss within 5 years.<sup>3</sup> However, PRP is difficult to administer in eyes with media opacities and may induce or exacerbate macular edema.<sup>4,5</sup> Additionally, PRP causes irreversible peripheral visual field loss and impairs night vision.<sup>6</sup> Moreover, most patients cannot tolerate complete PRP in one session, and therefore it is usually divided into two or more sessions.

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Neovessels may continue to grow after the first laser session and their regression can take weeks after PRP is completed.<sup>7</sup> Despite PRP, severe vitreous hemorrhage can occur in 4.5% of cases, requiring pars plana vitrectomy.<sup>8</sup>

Over the past decade, anti-vascular endothelial growth factor (anti-VEGF) agents have been playing a key role in the treatment of diabetic macular edema,<sup>9</sup> and recently there is a trend toward using anti-VEGF agents to treat PDR, but with limitations.<sup>10</sup> In contrast to PRP, the effect of anti-VEGF is transient, and we do not know how many injections are required to stabilize the retina.<sup>11,12</sup> While PRP requires several weeks to exert its full effect, the exact time required for neovascular regression following anti-VEGF is not yet determined.

The aim of this study is to determine the timing of neovascular regression after intravitreal bevacizumab 1.25 mg injection given as initial therapy for eyes with high-risk PDR without clinically significant macular edema (CSME). This may be useful in understanding the role of anti-VEGF agents in treating high-risk PDR without CSME.

## Patients and methods

### Study population

This study included patients who had at least one eye with high-risk PDR without CSME presenting consecutively to one vitreo-retinal specialist (FIS) at the vitreo-retinal clinic of Ibn Al-Haetham Teaching Eye Hospital (IAHTEH) in Baghdad, Iraq between October 2016 and January 2018, and adhered to the follow-up schedule of the study. Patients with type 1 or type 2 diabetes who were at least 18 years old of both genders were eligible for the study. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local institutional review board, the Scientific Committee of Ibn Al-Haetham Teaching Eye Hospital. All participants gave written informed consent before entering the study.

We defined high-risk PDR according to the Diabetic Retinopathy Study,<sup>13</sup> as any of the following: 1) neovascularization of the disc (NVD) greater than 1/4 disc area; 2) any NVD associated with vitreous or preretinal hemorrhage; or 3) neovascularization elsewhere (NVE) greater than 1/2 disc area associated with vitreous or preretinal hemorrhage. Exclusion criteria were: 1) history of previous vitrectomy; 2) history of previous laser retinal therapy; 3) history of previous intravitreal injection of anti-VEGF or steroids; and 4) media opacity (cataract or vitreous hemorrhage) that prevents good assessment of the fundus (site and size of neovascularization).

### Study design

This is a prospective uncontrolled interventional study.

### Treatment protocol

Participants were treated initially with intravitreal injection of bevacizumab (Avastin®; Genentech USA, Inc., South San Francisco, CA, USA) (1.25 mg in 0.05 mL) every 4 weeks until no neovessels were detected 4 weeks after the last injection. At this point, standard PRP was applied. Patients were examined 48 hours, 1, 2, and 4 weeks after each injection for funduscopy and assessment of neovascularization. At each examination, neovascularization was classified as complete regression, partial regression, or recurrence of neovascularization.

All participants underwent a detailed ophthalmologic examination, including Snellen chart best-corrected visual acuity, applanation tonometry, slit lamp examination of anterior segment of the eye including lenticular status, and fundus examination through a dilated pupil using slit lamp biomicroscopy with Volk +90 diopter lens. Fundus images were taken before treatment and during follow-up to document the state of neovascularization. Optical coherence tomography was performed to document central macular thickness in doubtful cases. All patients were sent for general laboratory investigations, including fasting blood sugar, glycated hemoglobin HbA1c, and serum lipid profile, and were referred to a specialist endocrinologist for management of their diabetes.

### Procedure

Following topical anesthesia with proparacaine eye drops, bevacizumab 1.25 mg in 0.05 mL was injected into the vitreous cavity via a 27-gauge needle inserted through the inferotemporal pars plana 3.5 mm posterior to the limbus, under sterile conditions in a theater room. Ciprofloxacin 0.3% eye drops four times daily were prescribed for 3 days after the procedure. For patients with bilateral high-risk PDR, intravitreal injections were given for both eyes simultaneously.

PRP was administered in two sessions, 2 weeks apart when there was complete regression of neovessels at 4 weeks following each injection. After complete PRP, follow-up visits and treatment were recommended according to the clinical condition of the eye.

### Outcomes

The primary objective of this study was to determine the timing of regression of neovessels following intravitreal

injection of bevacizumab. Our secondary objective was to detect neovascular recurrence following regression, incident macular edema, new vitreous hemorrhage, or development of tractional retinal detachment within 4 weeks following intravitreal bevacizumab injection.

We defined complete neovascular regression as complete absence of previously clinically active neovessels or complete absence of neovessels from previous fibrovascular membranes, leaving avascular membranes. We defined partial neovascular regression as decrease in the number or size of clinically active neovessels, and neovascular recurrence as development of neovessels after complete regression. Neovascular status was assessed by the first author (FIS) in all patients, and validated by the third author (SAA) in most patients. While fluorescein angiography was ordered as part of clinical care for some patients, neovascular status was only assessed clinically for this research, because of the financial and logistical impracticality of repeated angiographies. In patients with bilateral disease ( $n=3$ ), both eyes were included in the analysis.

## Results

Overall, 21 patients (24 eyes) with high-risk PDR without CSME treated initially with intravitreal bevacizumab 1.25 mg injections, adhered to the follow-up schedule and were included in the study. The baseline characteristics of these patients are summarized in Table 1. Of the 21 patients, 12 were male and nine were female. The mean age was 43.8 years (range: 23–52 years). Sixteen patients were on insulin injections, four patients were on oral hypoglycemic drugs, and one patient was on traditional medicine.

**Table 1** Demographic and clinical characteristics of study participants at baseline

Characteristic	Number of patients (%) (total =21)
Age (mean $\pm$ SD; range)	43.8 $\pm$ 5.4; 23–52
Gender	
Male	12 (57.1%)
Female	9 (42.9%)
Diabetes treatment	
Insulin	16 (76.2%)
Oral hypoglycemic drugs	4 (19.0%)
Traditional medicine	1 (4.8%)
HbA1c (range)	7.3%–14.2%
Hypertension <sup>a</sup>	3 (14.3%)
Current smoker	1 (4.8%)

**Note:** <sup>a</sup>Self-reported history of hypertension.

All patients had poorly controlled diabetes with elevated HbA1c (range: 7.3%–14.2%). Six eyes had NVD, 11 eyes had NVE, and seven eyes had both. Sixteen eyes had vitreous or pre-retinal hemorrhage that did not obscure fundus visualization or interfere with adequate assessment of the site and size of neovessels.

Forty-eight hours after intravitreal bevacizumab injection, we observed complete neovascular regression in 20 (83.3%) eyes, while the remaining four (16.7%) had partial regression. Neovascular regression was maintained (20 eyes with complete regression and four eyes with partial regression) during the first 2 weeks of follow-up. At the 4th-week visit, neovascularization recurred in three (12.5%) eyes that had initially shown complete regression. Additionally, neovascularization increased, in number and size, in the four eyes that had initial partial regression. At this time, we applied standard PRP to the 17 eyes with complete regression and administered a second bevacizumab injection in the seven eyes with persistent or recurrent neovascularization (Table 2).

Forty-eight hours after the second bevacizumab injection, six (86%) eyes showed complete and one (14%) showed partial regression. This response was again maintained for the subsequent 2 weeks. At the 4th-week visit, neovascularization recurred in one eye that had initially shown complete regression and regression was maintained in the remaining eyes (five complete, one partial regression). At this point, we performed standard PRP in the five eyes with complete regression, and administered a third injection of bevacizumab in the other two eyes (Table 2).

Following the third bevacizumab injection, we observed complete neovascular regression after 48 hours in both eyes. This response was maintained at 4 weeks, and standard PRP was applied (Table 2).

All eyes in the study maintained the same or attained better visual acuity. We observed no new vitreous hemorrhage, incident macular edema, or incident tractional retinal detachment during the study period.

## Discussion

Protocol S study of the Diabetic Retinopathy Clinical Research Network (DRCRnet), presented at American Academy of Ophthalmology 2015 annual meeting, concluded that Lucentis® (ranibizumab; Genentech, Inc., South San Francisco, CA, USA) is non-inferior to PRP at 2 years in patients with PDR with regard to visual acuity outcomes.<sup>10</sup> A disadvantage of using anti-VEGF as an alternative to PRP for PDR is transience of effect. Moreover, the cost of repeated

**Table 2** Neovascular status after each intravitreal bevacizumab 1.25 mg injection

Time of examination	Neovascular status	Bevacizumab injection		
		First injection (total =24)	Second injection (total =7)	Third injection (total =2)
		n <sup>a</sup> (%)	n <sup>a</sup> (%)	n <sup>a</sup> (%)
48 hours	Complete regression	20 (83.3%)	6 (85.7%)	2 (100%)
	Partial regression	4 (16.7%)	1 (14.3%)	0
1 week	Complete regression	20 (83.3%)	6 (85.7%)	2 (100%)
2 weeks	Complete regression	20 (83.3%)	6 (85.7%)	2 (100%)
4 weeks	Recurrence after complete regression	3 (12.5%)	1 (14.3%)	0
	Complete regression	17 (70.8%)	5 (71.4%)	2 (100%)

**Note:** <sup>a</sup>Number of eyes in each neovascular regression category.

injections, long-term follow-up, repeated hospital visits, and potential risk of endophthalmitis induced by repeated injections may outweigh the benefits of avoiding the side effects of PRP. In spite of its short duration, use of anti-VEGF for PDR is beneficial in a variety of clinical conditions such as media opacity, PDR with macular edema, as a preoperative adjunct for advanced diabetic retinopathy, and to induce rapid regression of iris neovessels in neovascular glaucoma secondary to PDR.<sup>14-17</sup>

This study illustrates that the action of bevacizumab starts shortly after intravitreal injection. When we administered bevacizumab 1.25 mg for high-risk PDR without CSME, the majority of neovessels regressed completely within 48 hours (83% after first injection and 86% after second injection). Previous studies reported the rapid resolution of neovascularization and vitreous hemorrhages after anti-VEGF injection.<sup>18,19</sup> However, to our knowledge, this is the first report to show regression of neovessels within 48 hours after intravitreal injection of bevacizumab. This rapid onset of action probably makes bevacizumab, and potentially other anti-VEGF agents, an ideal option to initially treat high-risk PDR, as severe vitreous hemorrhage can occur within the time period following PRP pending its onset of action.<sup>7,8</sup>

We systematically assessed patients at 48 hours, 1, 2, and 4 weeks, and we observed that no further regression of neovessels occurred after the first 48 hours. The observation of full bevacizumab effect after 48 hours has an important clinical implication: if only partial regression is detected 48 hours after bevacizumab injection, patients may benefit from another injection sooner than 4 weeks, which is the interval utilized in the Protocol S study.<sup>10</sup>

The maximal neovascular regressive effect of bevacizumab was maintained through the first 2 weeks. Thereafter, some eyes showed recurrence of neovessels (three [12.5%] eyes after the first injection, and one [14.3%] eye after the second injection).

The reported time of neovascular recurrence is variable in previous studies ranging between 1 week and 3 months.<sup>20-22</sup>

In this study, we applied standard PRP when eyes showed complete neovascular regression 4 weeks after bevacizumab injection to induce a more durable effect against neovascular recurrence and to avoid the side effects of repeated intravitreal injections. All neovascular recurrences occurred, in this study, after the 2-week visit, hence we suggest earlier application of PRP in eyes with complete neovascular regression following bevacizumab. Earlier PRP may protect against some neovascular recurrence after bevacizumab.

The combination of anti-VEGF and PRP has been used to treat PDR in recent studies to reduce the risk of macular edema after PRP,<sup>23-25</sup> or to treat persistently active neovessels refractory to PRP.<sup>26,27</sup> The 2017 Global Trends in Retina survey showed that 28.4% of retina specialists use a combination of anti-VEGF and PRP to manage high-risk PDR without macular edema.<sup>28</sup> However, there is no empirically agreed-upon regimen for this combined therapy.

We are limited in this study by small sample size and lack of a control group. Even though we lacked a control group, previous research has shown that neovascular regression takes weeks to months with PRP in PDR.<sup>7,29,30</sup> The time to neovascular regression in this study, with complete regression in more than 80% of eyes with high-risk PDR within 48 hours, is clearly more rapid than that shown for PRP. We only assessed neovascularization clinically because of the impracticality of repeated fluorescein angiography.

This study highlights the advantage of intravitreal bevacizumab as initial treatment of high-risk PDR without CSME to induce rapid neovascular regression. We believe the combination of anti-VEGF and PRP holds a promising role to treat high-risk PDR without CSME. Further research is required to determine the most appropriate interval between bevacizumab administration and PRP application.

## Conclusion

The majority of neovessels completely regressed within 48 hours after intravitreal injection of bevacizumab given as initial therapy for high-risk PDR without CSME. The full neovascular regressive effect occurred within 48 hours and was maintained for at least 2 weeks.

## Disclosure

The authors report no conflicts of interest in this work.

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