

Management of Florid Diabetic Retinopathy

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Abstract

Background: Florid diabetic retinopathy (FDR) is a severe form of proliferative diabetic retinopathy associated with high risk of blindness. **Aim:** The aim of this study is to evaluate the efficacy and safety of prompt intravitreal injection of bevacizumab followed by complete pan-retinal photocoagulation (PRP) for treating eyes with FDR. **Setting and Design:** Prospective, interventional case series. **Patients and Methods:** Patients with FDR were treated initially with intravitreal injections of bevacizumab 1.25 mg. One week after the injection, patients were sent for wide field fluorescein angiography (WFA), and PRP was performed in two sessions, 2 weeks apart. Patients were examined every 2–4 weeks to determine the status of new vessels (NVs). Additional laser burns were applied in cases with recurrence of NVs. **Statistical Analysis:** Numbers and percentages were calculated and reported. **Results:** Eleven patients (18 eyes) with FDR were included. All included patients had poorly controlled diabetes mellitus with mean glycated hemoglobin of 10.6%. One week after the injection, all eyes showed clinical regression of NVs. WFA showed extensive areas of peripheral retinal capillary nonperfusion. Eight weeks after the injection, three eyes (16.7%) showed recurrent increase in NVs, and additional laser therapy was performed for these eyes with special attention to ablating the areas of peripheral capillary non-perfusion. After 16 weeks from the primary treatment, 15 eyes (83.3%) had complete neovascular regression on clinical and angiographic assessment. Pars planavitrectomy was required for three eyes (16.7%) with tractional retinal detachment (2 eyes) or macular epi-retinal membranes (one eye). **Conclusions:** According to this study, most cases with FDR stabilized after prompt bevacizumab injection followed by complete PRP with special attention for ablating the peripheral capillary nonperfusion areas, guided by WFA images.

Keywords: Bevacizumab, diabetic retinopathy, vascular endothelial growth factor

INTRODUCTION

In 2014, the prevalence of diabetes mellitus in the world was about 9% among adults above age of eighteen years.^[1] Approximately 1.5% of adults with diabetes mellitus have proliferative diabetic retinopathy (PDR) with abnormal new vessels (NVs), either on the disc (NVD) or elsewhere (NVE).^[2]

Sometimes diabetic patients with poor metabolic control present with a severe form of PDR, with profuse NVs that extend several disc diameters in all directions. This severe form of high-risk PDR has been defined as florid, rapid, bloody, blinding diabetic retinopathy, and sometimes termed “coralliform” for its resemblance to sea corals.^[3-6] Florid diabetic retinopathy (FDR) typically has a fulminant course and poor prognosis with the high incidence of vitreous hemorrhage, retinal detachment, and blindness despite treatment with pan retinal photocoagulation (PRP).^[7-9]

The aim of this study is to evaluate the efficacy and safety of prompt intravitreal injection of bevacizumab (Avastin, Genentech, San Francisco, CA, USA) followed with complete PRP for treating eyes with FDR.

PATIENTS AND METHODS

This prospective, interventional case-series study included patients with FDR presented consecutively to two vitreo-retinal consultants (FIS) and (SAA), at the Vitreo-Retinal Clinic at Ibn Al-Haitham Teaching Eye Hospital in Baghdad, Iraq, between February 2018 and February 2019. The study protocol

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adhered to the tenets of the declaration of Helsinki. Ethical board approval was granted by the Scientific Committee of Ibn Al-Haitham eye hospital, and written informed consent was obtained from all participants.

The diagnosis of FDR was made on the clinical examination. In this study, FDR was defined as profuse arborization of neovessels (NVD and or NVE) extending several disc diameters in all directions. FDR may or may not be associated with preretinal or vitreous hemorrhage.

Patients with type 1 or type 2 diabetes mellitus, aged 18 years and older of both genders were eligible for the study. The exclusion criteria were: (1) history of laser retinal phototherapy, (2) history of vitrectomy, (3) history of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents injections or intravitreal steroids injections, (4) vitreous or pre-retinal hemorrhage that prevent good assessment of the fundus or applying complete PRP, and (5) tractional retinal detachment.

After complete history was taken, best-corrected visual acuity and intra-ocular pressures were recorded. A standard ophthalmologic examination was performed, including slit-lamp examination of the anterior segment, followed by dilated fundus examination using slit-lamp biomicroscopy with Volk +90 D lens. The presence of diabetic macular edema was diagnosed clinically or by optical coherence tomography.

Within 2 days after presentation, intra-vitreous Bevacizumab was given by one vitreoretinal specialist (SAA) at Ibn Al-Haitham Teaching Eye Hospital in a theater room under sterile conditions. After topical anesthesia, bevacizumab 1.25 mg in 0.05 mL was injected into the vitreous cavity through a 29 G needle inserted 3.5 mm posterior to the limbus. Patients were prescribed antibiotic eye drops for 3 days after the procedure. For patients with bilateral FDR, bevacizumab injections were given for both eyes simultaneously.

One week after the intravitreal injection, wide-field fluorescein angiography (WFA) with Optos camera (Optos, United Kingdom) was taken to document the presence of any leaking NVs and to assess the perfusion state of the retina. Laser treatment was performed, 1 week after the intravitreal injection using a frequency doubling Nd-YAG laser through a slit-lamp delivery system. Focal and diffuse macular edema was treated initially with focal or grid laser treatment according to the Early Treatment Diabetic Retinopathy Study protocol during the first PRP session.^[10-11] PRP was performed according to diabetic retinopathy study protocol.^[12] Complete PRP was performed in 2 sessions, 2 weeks apart from each other. Patients were then followed up every 2–4 weeks, and additional laser burns were applied in cases of clinical recurrence of NVs. After 16 weeks from the intravitreal injection, patients were sent for a second WFA to document the presence of any leaking NVs and to assess the perfusion state of the peripheral retina. After that follow-up and treatment were scheduled according to the clinical condition of the eye.

Main outcome measures were increase in vitreous hemorrhage, development of tractional retinal detachment, NVs regression, and stabilization of retinal vascularity.

In this study, clinical regression of NVs was defined as decrease in the number and size of NVs. Clinical recurrence of NVs was defined as recurrent increase in the number and or size of NVs. While stabilized retinal vascularity was defined as complete clinical and angiographic regression of NVs and absence of leakage of dye with WFA. Patients with tractional retinal detachment or significant epi-retinal membranes were scheduled for pars plana vitrectomy (PPV).

RESULTS

During the period of this study, a total number of 11 patients (18 eyes) with FDR were included. Seven patients (63.6%) presented with bilateral FDR, and four (36.4%) with unilateral FDR. While the other eye in the patients with unilateral FDR had either vitreous hemorrhage precluding fundus evaluation (one eye), or PDR that did not match the required inclusion criteria of FDR in this study (3 eyes). At presentation, 14 eyes had clinically significant macular edema. The baseline characteristics of patients are summarized in Table 1. Of the 11 patients, 6 were female and 5 were male. The mean age was 31.6 years (age range: 20–43 years). Eight patients (72.7%) were on insulin injections, and three patients were on oral hypoglycemic drugs. All included patients had poorly controlled diabetes with mean HbA1c was 10.6% (range 8.4–15.1).

The status of NVs is shown in Table 2. One week after the intravitreal injection, all eyes had NVs regression on clinical examination, while WFA revealed extensive areas of capillary nonperfusion in all cases, and late leakage of the dye from clinically regressed neovessels. At the same day (1 week after the intravitreal injection), PRP was performed to all eyes divided in 2 sessions 2 weeks apart, with specific attention to ablating the areas of peripheral capillary non-perfusion based on WFA images.

After 8 weeks from the intravitreal injection, 12 eyes (66.7%) maintained clinical NVs regression, while 3 eyes (16.7%)

Table 1: Clinical characteristics of the patients included in the study

Clinical characteristics	Number (%)
Number of patients	11
Mean age (range), years	31.6 (20–43s)
Gender (years)	
Female	6 (54.5%)
Male	5 (45.5%)
Insulin dependent diabetes mellitus	8 (72.2%)
Mean duration of diabetes mellitus (range), years	10.9 (5–17)
Mean HbA1c (range)	10.6% (8.4–15.1)
High blood pressure*	1 (12.5%)
Current heavy smokers**	1 (12.5%)

*Self-reported history of hypertension, **10 or more cigarettes per day

Table 2: Status of neovascularization in eyes with florid diabetic retinopathy

Time of examination	NVs status	Number of eyes (%)	Treatment
At presentation	FDR	18	Bevacizumab intravitreal injection
After 1 week	Clinical NVs regression*	18 (100)	WFA + PRP
After 8 weeks	Clinical NVs regression	12 (66.7)	
	Clinical recurrence of NVs**	3 (16.7)	Add-on laser therapy
	Tractional retinal detachment	2 (11.1)	PPV
	Macular epi-retinal membrane	1 (5.6)	PPV
After 16 weeks	Stabilized retinal vascularity***	15 (83.3)	WFA
	Number of eyes required PPV	3 (16.7)	

*Clinical decrease in the number and size of NVs, **Clinical recurrent increase in number and or size of NVs, ***Flat retina with complete NVs regression and no leakage of dye in WFA. WFA: Wide field fluorescein angiography, PRP: Pan-retinal photocoagulation, PPV: Pars plana vitrectomy, NVs: Neovascularizations, FDR: Florid diabetic retinopathy

showed recurrence of NVs. Additional laser therapy was performed for eyes with recurrent NVs, with specific attention for complete ablating of the areas of peripheral capillary non-perfusion identified by WFA images. Two eyes had localized tractional retinal detachment at the site of previous retinal neovascularization, and one eye had macular epi-retinal membranes. None of the patients treated with primary bevacizumab had increase in vitreous hemorrhage.

After 16 weeks from the initial treatment, repeated WFA was performed and 15 eyes (83.3%) had stabilized retinal vascularity, whereas PPV was done in the remaining three eyes (16.7%). Two of them developed tractional retinal detachment and one eye developed macular epiretinal membranes. Further management and follow-up were scheduled according to the individual clinical condition.

DISCUSSION

FDR usually occurs in poorly controlled young diabetic patients, more in females, with bilateral affliction.^[5,6] In the current study, the mean age of the patients with FDR was 32.6 years, from both genders, and about two thirds of patients presented with bilateral FDR. All patients were poorly controlled diabetes with high HbA1c, and the majority (72.7%) was on insulin injections.

This condition is thought to occur secondary to diffuse retinal ischemia with widespread blood-retinal barrier breakdown.^[4] Poorly controlled diabetes with the episodes of acute hypoglycemic and transient increases in the serum levels of insulin-like growth factor 1 (IGF-1), along with increases in vitreous levels of VEGF are postulated to underlie the development of FDR.^[13] In this study, all cases showed extensive areas of capillary nonperfusion involving the retinal periphery on WFA.

FDR has a rapid course with high risk of blinding complications occur in a short time despite treatment.^[5,6,8] In the 1960s and early 1970s, pituitary ablation was the treatment of choice to preserve vision for this group of patients.^[3] Latter, use of extensive PRP, pars-plana vitrectomy after photocoagulation, and intravitreal injections of triamcinolone acetonide or

bevacizumab adjunct to PRP were considered to limit blindness in FDR.^[5-7,14]

Recently, there is an increasing role for using anti-VEGF agents to treat PDR.^[15-17] In the current study, patients with FDR received prompt intravitreal Bevacizumab injection. After 1 week, all cases had the clinical signs of NVs regression. Intravitreal injection of anti-VEGF has a rapid action on NVs regression, and a previous study, showed that the majority of NVs regressed clinically within 48 h after bevacizumab injection.^[18] While complete PRP, requires several weeks to exert its full effect on NVs regression.^[19] NVs in FDR are extensive, and severe vitreous hemorrhage is more liable to occur before the complete action of PRP is achieved. In addition, applying complete PRP is more difficult in FDR because of the extended area of NVs that should be avoided when applying laser burns. In this study, no case had increase in vitreous hemorrhage after bevacizumab injection. Prompt intravitreal Bevacizumab injection carries less complications with vitreous hemorrhage, and probably is less likely to require vitrectomy surgery compared with prompt PRP.^[12]

The disadvantage of using anti-VEGF as monotherapy is its short-effect duration as retinal NVs tend to recur after a single intravitreal injection of anti-VEGF.^[20-22] A previous study showed that the maximum neovascular regressive effect of bevacizumab was maintained through the first 2 weeks after injection.^[18] Therefore, for patients with FDR, it is better to start treatment with bevacizumab (or possibly other type of anti-VEGF agents) for its rapid action on NVs regression, followed by standard PRP for a more durable effect.^[18] In addition, it is probably better to apply early PRP (within 2 weeks) after intravitreal injection of bevacizumab during the period of maximum effect of anti-VEGF on NVs regression.^[18]

FDR occurs in poorly controlled DM, and recurrence of NVs may occur after PRP, that requires close follow-up and addition of laser burns. Probably, complete PRP with specific attention for ablating the peripheral capillary nonperfusion areas with laser burns may reduce the secretions of VEGF and the recurrence of NVs.

After 16 weeks from starting treatment, 15 eyes (83.3%) with FDR had stabilized retinal vascularity and did not require surgery.

In this study, as in other previous studies, FDR was defined as an aggressive type of PDR, the NVs are profuse and extend several disc diameters in all directions.^[6,7,12] Further studies with longer-term follow-up and a new definition of FDR, regarding the size and the extent of the NVs are probably required.

CONCLUSIONS

According to this study, most cases with FDR (83.3%) stabilized after prompt Bevacizumab injection followed by complete PRP with special attention for ablating the peripheral capillary non-perfusion areas, guided by WFA images.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Global Status Report On Noncommunicable Diseases 2014. Geneva: World Health Organization, 2014.
- Zhang X, Saaddine JB, Chou CF, Cotch MF, Cheng YJ, Geiss LS, *et al.* Prevalence of diabetic retinopathy in the United States, 2005-2008. *JAMA* 2010;304:649-56.
- Kohner EM, Hamilton AM, Joplin GF, Fraser TR. Florid diabetic retinopathy and its response to treatment by photocoagulation or pituitary ablation. *Diabetes* 1976;25:104-10.
- Lattanzio R, Brancato R, Bandello FM, Azzolini C, Malegori A, Mastranzi G. Florid diabetic retinopathy (FDR): A long-term follow-up study. *Graefes Arch Clin Exp Ophthalmol* 2001;239:182-7.
- Ahmad SS, Ghani SA. Florid diabetic retinopathy in a young patient. *J Ophthalmic Vis Res* 2012;7:84-7.
- Agardh E. Rapid, bloody, and blinding diabetic retinopathy. *Acta Ophthalmol* 2010;88:274-8.
- Favard C, Guyot-Argenton C, Assouline M, Marie-Lescure C, Pouliquen YJ. Full panretinal photocoagulation and early vitrectomy improve prognosis of florid diabetic retinopathy. *Ophthalmology* 1996;103:561-74.
- Ahmad SS, Ghani SA, Alexander SM. Successful management of a patient with florid diabetic retinopathy. *Int J Ophthalmol Eye Res* 2016;4:220-3.
- Burak TM. Florid retinopathy: A rapidly progressive form of proliferative diabetic retinopathy. *Adv Ophthalmol Vis Syst* 2018;8:221-2.
- Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. *Ophthalmology* 1987;94:761-74.
- Olk RJ. Modified grid argon (blue-green) laser photocoagulation for diffuse diabetic macular edema. *Ophthalmology* 1986;93:938-50.
- The Diabetic Retinopathy Study Research Group: Indications for photocoagulation treatment of diabetic retinopathy. Diabetic Retinopathy Study Report Number 14. *Invest Ophthalmol Clin* 1994;27:239-53.
- Kitano S, Funatsu H, Tanaka Y, Suzuki M. Vitreous levels of IGF-1 and VEGF in florid diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2005;46:347.
- Rizzo S, Genovesi-Ebert F, Di Bartolo E, Vento A, Miniaci S, Williams G. Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR). *Graefes Arch Clin Exp Ophthalmol* 2008;246:837-42.
- Figueira J, Fletcher E, Massin P, Silva R, Bandello F, Midena E, *et al.* Ranibizumab Plus Panretinal Photocoagulation versus Panretinal Photocoagulation Alone for High-Risk Proliferative Diabetic Retinopathy (PROTEUS Study). *Ophthalmology* 2018;125:691-700.
- Zhao Y, Singh RP. The role of anti-vascular endothelial growth factor (anti-VEGF) in the management of proliferative diabetic retinopathy. *Drugs Context* 2018;7:212532.
- Shah GK, Stone TW, editors. Global Trends in Retina Survey. Chicago, IL: American Society of Retina Specialists; 2017.
- Shakarchi FI, Shakarchi AF, Al-Bayati SA. Timing of neovascular regression in eyes with high-risk proliferative diabetic retinopathy without macular edema treated initially with intravitreal bevacizumab. *Clin Ophthalmol* 2019;13:27-31.
- Vander JF, Duker JS, Benson WE, Brown GC, McNamara JA, Rosenstein RB. Long-term stability and visual outcome after favorable initial response of proliferative diabetic retinopathy to panretinal photocoagulation. *Ophthalmology* 1991;98:1575-9.
- Wubben TJ, Johnson MW. Anti-VEGF Treatment Interruption Study Group. Anti-vascular endothelial growth factor therapy for diabetic retinopathy: Consequences of inadvertent treatment interruptions. *Am J Ophthalmol* 2019;204:13-8.
- Ishikawa K, Honda S, Tsukahara Y, Negi A. Preferable use of intravitreal bevacizumab as a pretreatment of vitrectomy for severe proliferative diabetic retinopathy. *Eye (Lond)* 2009;23:108-11.
- Thew M. Rapid resolution of severe retinal neovascularisation in proliferative diabetic retinopathy following adjunctive intravitreal bevacizumab (Avastin). *Clin Exp Optom* 2009;92:34-7.