

Original Research Article

Fundus fluorescein angiographic assessment of patients with proliferative diabetic retinopathy and macular edema before and after intravitreal injection of Bevacizumab

Ankur¹, Yogesh Kumar*², Deepesh Arora³, Rupali Tyagi⁴, Sanjeev Kumar Mittal⁵

¹Department of Ophthalmology Adesh Medical College and Hospital, Mohri, Shahbad, Ambala, Haryana, India

²Department of Ophthalmology SHKM, Government Medical College, Nuh, Haryana, India

³Consultant Amritsar Eye Clinic East Canal Road, Dehradun, Uttarakhand, India

⁴Department of Ophthalmology Shri Guru Ram Rai Institute of Medical and Health Sciences Dehradun, Uttarakhand, India

⁵Department of Ophthalmology AIIMS, Rishikesh, Uttarakhand, India

Received: 11 August 2019

Revised: 13 September 2019

Accepted: 26 September 2019

*Correspondence:

Dr. Yogesh Kumar,

Email: eyeologist@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: To assess the role of intravitreal bevacizumab (1.25 mg) in patients with proliferative diabetic retinopathy with macular edema in terms of change in leakage area and best-corrected visual acuity.

Methods: This prospective randomized interventional study was conducted in the Department of Ophthalmology from September 2013 to August 2015 and included thirty eyes of twenty patients.

After a detailed history and ocular examination, diagnosed cases of proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) underwent sequential fundus fluorescein angiography. Bevacizumab was administered intravitreally. Patients were assessed two hours after injection for anterior chamber reaction and intraocular pressure and were advised follow-ups at 24 hours and then at 1, 4, 8 and 12 weeks. For the outcome, the change of retinal new vessels by assessment of leakage area using Quantitative Planimetric Analysis (QPA) of photographs as well as the change in best-corrected visual acuity (BCVA) from baseline to the 12 weeks follow-up, were done. Results were analyzed statistically by applying t-test.

Results: Intravitreal bevacizumab injection lead to a significant decrease in leakage in DME and PDR, and improvement in mean BCVA. The effect was maximum at 4 weeks which weaned off as the study progressed through it remains statistically significant at the end of 12 weeks.

Conclusions: Intravitreal bevacizumab plays a major role in treating and reducing visual deterioration in patients with proliferative diabetic retinopathy and diabetic macular edema.

Keywords: Diabetic retinopathy, Fluorescein angiography neovascularization, Intravitreal bevacizumab, Macular edema

INTRODUCTION

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia.¹ The American Diabetic Association broadly classifies

Diabetes mellitus as type 1, and type 2 Diabetes mellitus. Other forms of diabetes including genetically mediated, secondary to endocrinopathies and drug or chemical induced, have also been recognized.² Currently the number of cases of diabetes worldwide is estimated to be

around 347 million; of these 90% are type 2 diabetes. The population of India has an increased susceptibility to diabetes mellitus. During the year 2004, there were estimated 37.7 million cases of diabetes in the country, of these 21.4 million were in urban areas and 16.3 million in rural areas.³

Chronic complications of diabetes can be divided into vascular and nonvascular complications. The vascular complications are further subdivided into microvascular (retinopathy, neuropathy and nephropathy) and macrovascular complications e.g. coronary artery disease (CAD), peripheral arterial disease (PAD) and cerebrovascular disease.⁴

Diabetic retinopathy is progressive dysfunction of the retinal vasculature caused by chronic hyperglycemia resulting in structural damage to the neural retina.⁵ Individual with diabetes mellitus is 25 times more likely to become legally blind than individuals without diabetes mellitus.⁴ Diabetic retinopathy changes are classified as non-proliferative (NPDR), proliferative diabetic retinopathy (PDR), and diabetic macular edema (DME). Imaging modalities used for diagnosis are fundus photography, optical coherence tomography and fundus fluorescein angiography (FFA).⁶

Ocular treatment of diabetic retinopathy (NPDR, PDR, DME) includes scatter laser photocoagulation/ pan-retinal photocoagulation/focal or grid photocoagulation, intravitreal anti-angiogenic factors (anti-vascular endothelial growth factor agents), and intravitreal corticosteroids, vitreolysis by intravitreal injection of tissue-plasminogen activator to bring complete posterior vitreous detachment or liquefaction of vitreous gel and vitrectomy for non-clearing vitreous hemorrhage, tractional or progressive retinal detachment and macular edema with epiretinal proliferation, tangential traction or taut posterior hyaloids.^{6,7}

Proliferative diabetic retinopathy (PDR) and Diabetic macular edema (DME) are major cause of visual loss in diabetic patients. In PDR and DME, vascular endothelial growth factor (VEGF) is known to play a key role in the growth of new vessels from the retina or optic nerve since VEGF is thought to be released into the vitreous cavity in response to ischemia. Because VEGF has been shown to play a major role in retinal neovascularization, although other factors may be involved as well, anti-VEGF treatments have been hypothesized as an alternative adjunctive treatment for retinal neovascularization.⁸⁻¹⁴

Bevacizumab (Avastin TM Genentech Inc., San Francisco, CA, USA) is a complete full-length humanized antibody that binds to all subtypes of VEGF and is successfully used in tumor therapy as a systemic drug.¹⁵

Recently, several case reports and small-scale clinical trials provided evidence that intravitreally administered

anti-VEGF drugs may induce a short-term regression of new vessels in vasoproliferative disease. Regression of optic disc neovascularization was demonstrated after intravitreal injection of the anti-angiogenic agent bevacizumab in the setting of diabetic retinopathy. Nevertheless, this effect seems to be transient as retinal neovascularization tended to recur by 12 weeks after a single intravitreal injection of bevacizumab.¹⁶

This study was conducted to evaluate the efficacy of bevacizumab in diabetic macular edema and proliferative retinopathy with use of Fundus Fluorescein Angiography (FFA) in terms of reduction in leakage area and improvement in BCVA.

METHODS

This prospective randomized interventional study was conducted in the Department of Ophthalmology, Shri Guru Ram Rai Institute of Medical and Health Sciences, after getting the approval of the Institutional Ethics Committee (IEC).

The patients visiting outdoor patient department (OPD) and diagnosed as a case of diabetic retinopathy were included and a written informed consent was taken. The study was conducted from September 2013 to August 2015. Thirty eyes of twenty patients were included.

Inclusion criteria

All patients of proliferative diabetic retinopathy with diabetic macular oedema were included in the study.

Exclusion criteria

- Any ocular pathology obscuring the view of fundus.
- Only focal macular edema attributable to focal leaks from micro aneurysm.
- Presence of any other macular pathology like age related macular degeneration (ARMD) or any vascular occlusive diseases affecting macula.
- Optic disc pathology due to chronic glaucoma.
- Previously treated with pan-retinal photocoagulation (PRP) and grid laser within last six months.
- Patients with evidence of vitreomacular traction.
- Angiographic evidence of widening or irregularity of the foveal avascular zone (FAZ) suggestive of ischemic maculopathy.
- Patients who didn't turn up for follow up till 12 weeks following intravitreal injection of avastin (bevacizumab).

Procedure

- All the patients were subjected to detailed history and ocular examination i.e. visual acuity

assessment (BCVA), applanation tonometry, slit-lamp examination, dilated indirect ophthalmoscopy and fundus photography.

- BCVA was recorded via early treatment diabetic retinopathy study (ETDRS) chart and changed to log units for calculation purpose.
- Intra ocular pressure was recorded using applanation tonometer.
- Slit lamp examination was performed to rule out anterior segment pathology i.e. presence or absence of cataract, iris neovascularisation and any media opacity obscuring the view of fundus.
- Dilated slit lamp biomicroscopy was performed using +78 D lens and indirect ophthalmoscopic examination was also done for fundus examination.
- Patient also underwent Investigations like blood pressure, random, fasting, and postprandial blood sugar, and glycosylated haemoglobin (HbA1c) levels.
- Fundus photographs of diagnosed cases of diabetic retinopathy were taken in color and red free filter, and subsequently fundus fluorescein angiography was done after taking written and informed consent.
- Medical fitness before intravitreal avastin for patients with PDR with macular edema was taken.
- The intravitreal injection of 1.25 mg of bevacizumab (Avastin 100 mg / 4mL vial, Genantech Inc, San Francisco, USA) in a volume of 0.05 mL solution was administered intravitreally in supero-nasal or temporal quadrant through pars plana by 26-gauge needle at a distance of 4 or 3.5mm in phakic or pseudophakic eyes, under topical (paracaine) anesthesia.
- The injections were given in the operating room under microscope after povidone-iodine eye preparation.
- Patients were assessed 2 hr after injection for anterior chamber reaction and IOP with non-contact tonometer.
- After 24 hours and one week later, reassessment was done by BCVA, applanation tonometry, slit lamp examination and slit lamp biomicroscopy.
- At 4 weeks, 8 weeks and 12weeks, patients were again subjected to detailed ocular examination.
- As outcome measures, the change of retinal new vessels by means of leakage area and the change in BCVA from baseline to the 12 weeks follow-up, were evaluated.
- To assess the leakage area in FFA Quantitative Planimetric Analysis (QPA) of photographs was done at 4, 8 and 12 weeks. Best photographs of late phases were chosen of around 8-10 minutes and were exported to personal computer for analysis. For area calculation software “able image analyzer”2001-2012 by mulabs.com was employed. Vertical diameter of disc was marked

and taken as a unit and to avoid inter-observer variation single retinal specialist demarcated leakage area. The area was calculated in units.

- A secondary end-point was the change in visual acuity during the same follow-up.
- Results were analyzed statistically applying t-test. Statistical analysis was done using Program Name: IBM SPSS Statistics Premium Grad Pack 20.0 Program Number: 5725-A54 software for windows.

RESULTS

Demographic profile of patients: This study comprised 30 eyes of 20 patients; thirteen were males, and seven were females with male to female ratio of 1.86:1. All patients were of type 2 diabetes mellitus. The age ranged from 51-81, with a mean age of 61.1. All patients had proliferative diabetic retinopathy with diabetic macular edema. Eight patients (ten eyes) had NVD in which three were female (three eyes) and five were males (seven eyes). Fifteen patients (20 eyes) had NVE in which ten were males (13 eyes) and five were females (seven eyes).

Duration of diabetes varied from 6 months to more than 20 years. Four patients (7 eyes) had history of diabetes of duration of 0-5 year, 8 patients (10 eyes) had history of 6-10 years, 6 patients (9 eyes) had history of 11- 15 years and 2 patients (4 eyes) had history of more than 15 years. Mean duration of diabetes was 9.43 years. HbA1c was measured and mean HbA1c was 7.06±1.015.

Table 1: Distribution of HbA1c level among patients

HbA1c	<6	6-7	7-8	>8
Number of patients	1 (2 eyes)	9 (13 eyes)	7 (10 eyes)	3 (5 eyes)
Males	0	7 (11 eyes)	4 (5 eyes)	2 (4 eyes)
Females	1 (2 eyes)	2 (2 eyes)	3 (5 eyes)	1 (1eye)

Effect of intravitreal avastin on leakage area in DME and Neovascular area (NVA), and BCVA. There was significant reduction in leakage area in DME and NVA following the use of intravitreal avastin.

There was significant improvement in BCVA following the use of intravitreal avastin. BCVA at presentation varied from 1.602 logMAR (etdrs acuity-1/40) to 0.398 logMAR (etdrs acuity - 4/10) with mean BCVA 0.867±0.240 logMAR (etdrs acuity~ 4/32). Post avastin mean BCVA was 0.299±0.285Logmar (etdrs acuity~4/8) at 4 weeks, 0.388±0.256 logMAR (etdrs acuity~4/10) at 8 weeks and 0.519±0.252 logMAR (etdrs acuity~4/12.5) at 12 weeks. Twenty-six eyes gained 2 etdrs lines at last (12 week) follow up and in 4 eyes there was no gain in visual acuity.

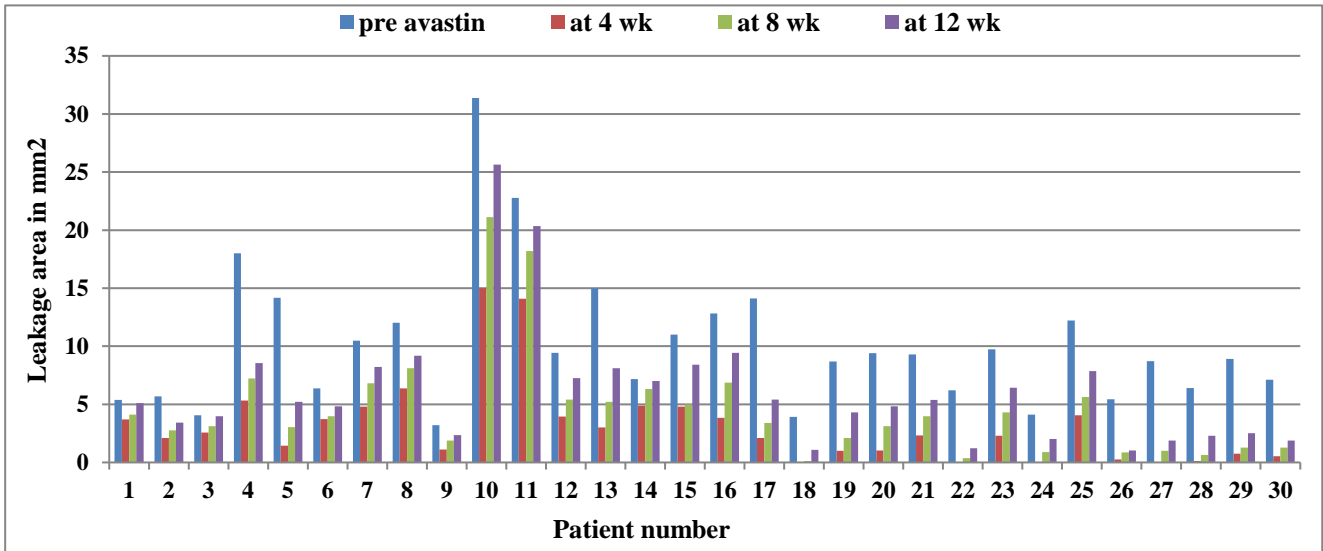


Figure 1: Leakage area (mm²) of dme in individual patients before avastin and at 4,8 and 12 weeks postavastin.

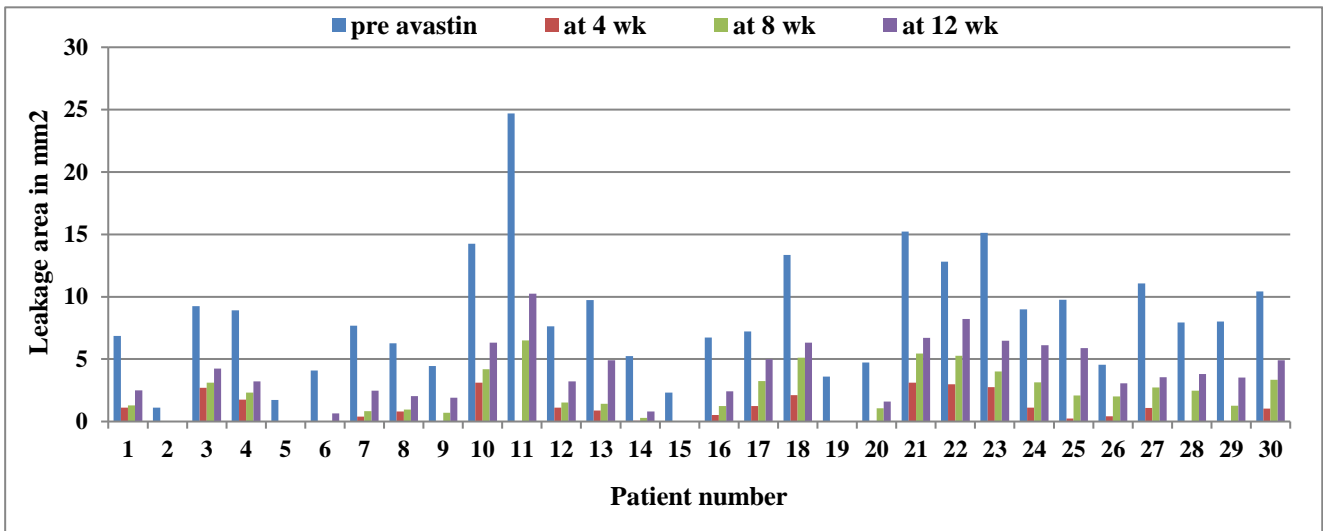


Figure 2: Leakage area of NVA in individual patients before avastin and at 4, 8 and 12 weeks postavastin.

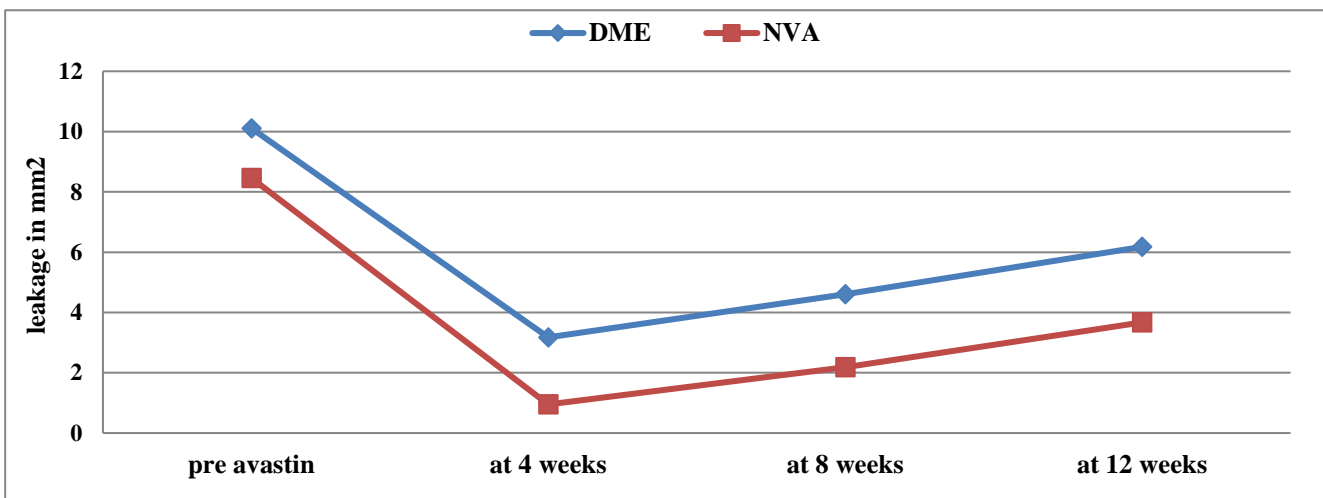


Figure 3: Mean leakage area (mm²) of DME and NVA before avastin and at 4, 8 and 12 weeks post-avastin.

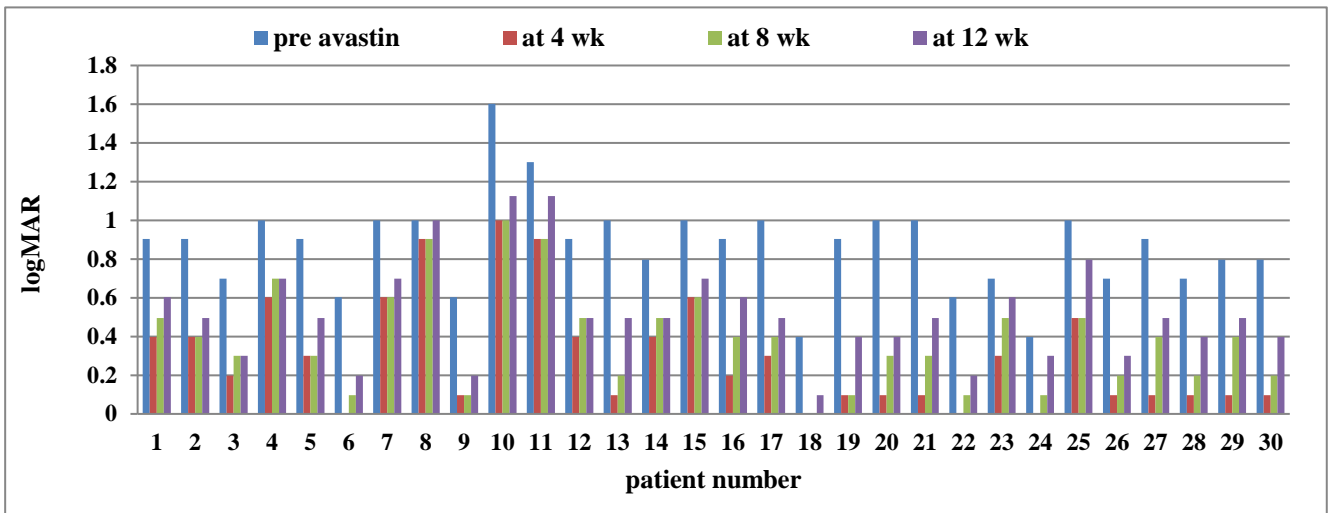


Figure 4: BCVA of individual patients in logMAR before avastin and at 4, 8 and 12 weeks after avastin.

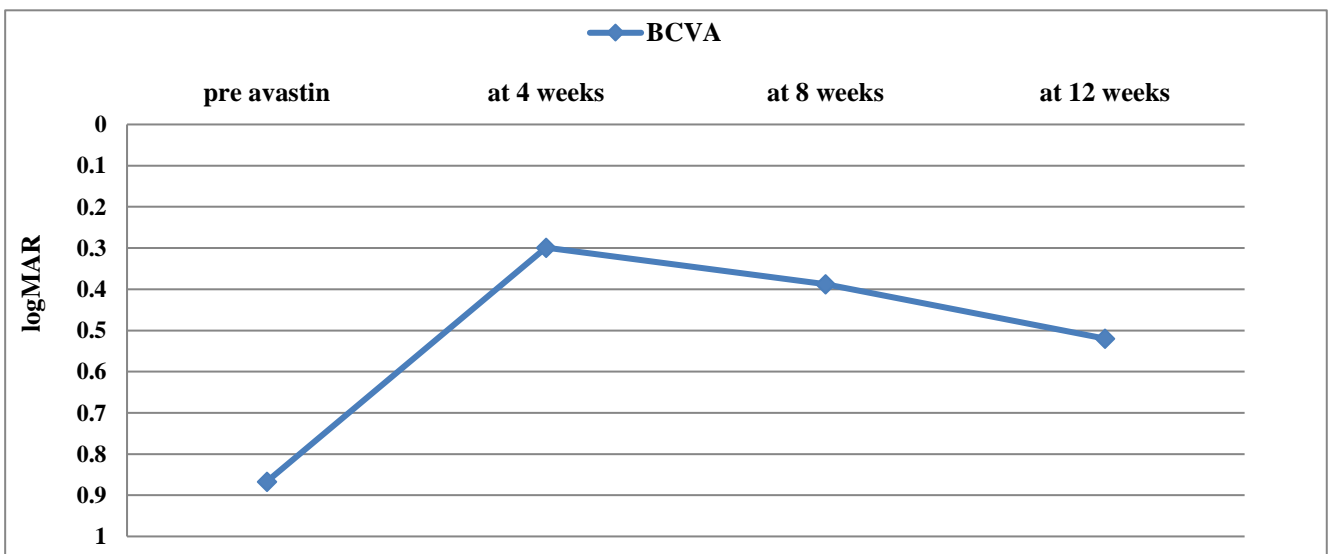


Figure 5: Mean BCVA in terms of logMAR before avastin and at 4, 8 and 12 weeks post-avastin.

No patient showed decline in visual acuity. By applying t- test and taking $P < 0.05$ for results, reduction in leakage in DME and NVA and gain in visual acuity was found to be statistically significant.

DISCUSSION

Diabetic macular edema and proliferative diabetic retinopathy are leading causes of blindness and visual deterioration in patients of diabetic retinopathy. In order to assess the efficacy of intravitreal bevacizumab (1.25 mg) in cases of PDR with DME, authors quantify the decrease in leakage following intravitreal bevacizumab injection at 4, 8 and 12 weeks by means of quantitative planimetric analysis of leakage of fluorescein dye in FFA and by gain in visual acuity.

There was significant decrease in DME (on angiogram) following intravitreal injection and maximum decrease

was noted at 4 weeks following injection. There was rebound increase in leakage at 8 weeks, which further increased at 12 weeks, but even at this last follow up i.e. 12 weeks decrease in leakage was statistically significant. (Figure 1 and 3) In previous studies, minimum or no leakage on FFA has been reported in patients with DME at 6 weeks follow up post intravitreal bevacizumab and in some at 4 weeks follow-up. There is recurrence of leakage after this, which increases with every follow up but remain significant by at least 12 weeks follow up. Similar pattern of decrease and recurrence in DME was noted on OCT at similar follow-ups. In many longer studies bevacizumab has been re-injected either as 4 or 6 weekly regimens or as needed. They showed improved or maintained edema at longer follow-ups. Some studies also used it in combination with laser with improved success and some in DME refractory to other treatment modalities with success.¹⁷⁻²¹

In the present study, leakage from neovascular area significantly decreased following intravitreal injection of bevacizumab on angiogram and was minimum at 4 weeks. Authors found an increase in leakage area similar to rebound increase in leakage area in DME at 8 weeks and this leakage area also further increased at 12 weeks, but net decrease remain statistically significant at 12 weeks. (Figure 2 and 3) In many previous studies, leakage from neovascular area on FFA has been documented to be minimum at 6 weeks and in some studies at 4 weeks post intravitreal bevacizumab follow up. There was weaning off of the effect of bevacizumab and concurrent recurrence of leakage after it, which increased with every follow up but remain significant by at least 12 week follow up. Longer studies in which it has been re-injected either as 4 or 6 weekly regimen or when required showed improved or maintained status at longer follow-ups. Some studies also used it in combination with laser with improved success and in cases of vitreous hemorrhage where PRP is not possible or in cases of failure of PRP with success.²²⁻²⁶

This study revealed maximum gain in BCVA at 4 weeks during the follow up period of 12 weeks. It declined at 8 weeks and further at 12 weeks, which corresponds to the leakage variation in DME at macula area. The gain in BCVA still remains statically significant at 12 weeks. At 12 weeks, 26 eyes showed gain in visual acuity by 2 etdrs lines and in 4 eyes it remained same, no patient showed decline in visual acuity. (Figure 4 and 5) The mean BCVA roughly corresponds to leakage present at macula due to diabetic macular edema. (Figure 3 and 5) This result were in concordance with previous studies, which reported the best BCVA at 4 to 6 weeks follow up with decreased improvement subsequently. In longer studies reinjection of bevacizumab has been used either as 4 or 6 weekly, with success in improvement or maintenance in visual acuity. In combination with other treatment modalities i.e. laser it was found to be useful. BCVA in previous studies roughly corresponded to leakage present at macula due to diabetic macular edema but also depend on visual acuity at present.^{27,28}

The results of this study as well as previous studies showed significant short-term improvement around 4 to 6 weeks, with slow weaning off of effect of bevacizumab intravitreal injection in DME, PDR and BCVA. Although effect of bevacizumab remained significant even after 3 months in this study, and longer as found in other longer studies. The recurrence occurred after a variable duration of time for both DME and PDR along with deterioration of BCVA. In different long duration studies, it has been used more than once, as monthly, 6 weekly or as per needed regimen, with constant success and maintaining or improvement of BCVA for long follow-ups. It had also been used in cases where the conventional therapy of PRP in PDR or grid or focal laser for DME fails to resolve them, or not possible like in cases of vitreous hemorrhage. Success was noted in all such cases.^{17-19,21-24}

Pan retinal photocoagulation (PRP) is currently the principal therapy for PDR, unless the patient already has extensive vitreous hemorrhage, which would preclude the possibility of laser photocoagulation. Neovascularization at disc (NVD) and vitreous hemorrhage were found to be more frequently associated with severe visual loss despite PRP in the Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS).

Long intervals between PRP sessions and the variable amount of time required for a favorable response may increase the incidence of complications due to the progression of PDR. In fact, a single episode of PRP or shorter intervals between PRP episodes, although desirable in severe PDR, is often associated with acute visual disturbances due to exudative choroidal detachment, retinal detachment, and macular oedema.^{22-24,28-30}

In contrast to PRP, intravitreal bevacizumab is shown to have a very safe local and systemic profile. This study and most of the above referenced studies showed no ocular or systemic complication occurring during follow up. There are some noted complications like endophthalmitis and tractional retinal detachment and exudative retinal detachment or choroidal detachment, but their frequency of occurrence is quiet low making it a safer and more effective alternative to laser treatment.^{18,19,24,25,29,30}

Thus, intravitreal bevacizumab is a strong competitor for first line of treatment for DME and PDR in future. Many studies have used bevacizumab in combination with laser photocoagulation (PRP or scatter or focal or grid) in PDR or DME and documented similar or slightly better outcomes by different assessment parameters. Others used it in different regimens like monthly or 6 weekly or as required with a controversial output and some other evaluated bevacizumab for different intravitreal doses with no significant outcome. As bevacizumab effect is short lasting, therefore its combination with other treatment modalities, its regimen, dosage and side effects are yet to be determined by longer and larger studies for the best outcome in patients. As it is a recent approach for treatment of diabetic retinopathy it had to pass the test of time to prove it. Limitations of this study was to Short follow up time, less sample size and no control sample.

CONCLUSION

There was significant decrease in leakage in DME and PDR, and improvement in mean BCVA after intravitreal bevacizumab, concluding its major role in treating and reducing visual deterioration in patients with DME and PDR.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Powers AC. Diabetes Mellitus. In: Kasper DL, Fauci AS, Longo DL, Hauser SL, Jameson JL, Loscalzo J, Editors. vol.2. Harrison's principles of internal medicine, 19th ed. New York: McGraw-Hill;2015:2399.
2. Retinal Vascular Disease: Diabetic Retinopathy. Retina and Vitreous (sec. 12). In: American Academy of Ophthalmology: Basic and Clinical Science Course, 2012-2013 Ed. San Francisco: Life Long Education for the Ophthalmologist; 2012:89.
3. Park K. Epidemiology of Non-Communicable Diseases. In: Park K, editor. Textbook of Preventive and Social Medicine, 23rd Ed. Jabalpur: Banarsidas Bhanot; 2015:393.
4. Powers AC. Complications of Diabetes Mellitus. In: Kasper DL, Fauci AS, Longo DL, Hauser SL, Jameson JL, Loscalzo J, Editors: vol.2 Harrison's principles of internal medicine, 19th Ed. New York: McGraw-Hill; 2015:2422-2424.
5. Limb LL, Rosenblatt BJ, Benson WE. Diabetic Retinopathy. In: Yanoff M, Duker J, Augsburger J, editors. Ophthalmology, 4th Ed. Edinburgh: Elsevier Saunders; 2014:541.
6. Wiley HE, Ferris III FL. Nonproliferative Diabetic Retinopathy and Diabetic Macular Edema. In: Schachat AP, Sadda SR, editors. Medical Retina (vol.2.). In: Ryan SJ, Editor. Retina, 5th Ed. London: Elsevier saunders; 2013:940-964.
7. Silva PAS, Cavallerano JD, Sun JK, Blodi BA, Davis MD, Aiello LM et al. Proliferative Diabetic Retinopathy. In: Schachat AP, Sadda SR, editors. Medical Retina (vol.2). In: Ryan SJ, editor. Retina, 5th Ed. London: Elsevier saunders; 2013:969-997.
8. Adamis AP, Miller JW, Bernal MT, D'Amico DJ, Folkman J, Yeo TK, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol.* 1994;118(4):445-50.
9. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med* 1994; 331: 1480-87.
10. Pe'er J, Shweiki D, Itin A, Hemo I, Gnessin H, Keshet E. Hypoxia-induced expression of vascular endothelial growth factor by retinal cells is a common factor in neovascularizing ocular diseases. *Lab Invest.* 1995;72:638-45.
11. Watanabe D, Suzuma K, Suzuma I, Ohashi H, Ojima T, Kurimoto M et al. Vitreous levels of angiopoietin 2 and vascular endothelial growth factor in patients with proliferative diabetic retinopathy. *Am J Ophthalmol.* 2005;139:476-81.
12. Tolentino MJ, McLeod DS, Taomoto M, Otsuji T, Adamis AP, Luttly GA. Pathologic features of vascular endothelial growth factor-induced retinopathy in the nonhuman primate. *Am J Ophthalmol.* 2002;133:373-85.
13. Adamis AP, Altaweel M, Bressler NM, Cunningham Jr ET, Davis MD, Goldbaum M et al. Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals. *Ophthalmology.* 2006;113:23-8.
14. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina.* 2006;26:275-8.
15. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov.* 2004;3:391-400.
16. Filho J, Messias A, Almeida F, Ribeiro J, Costa R, Scott I et al. Panretinal photocoagulation (PRP) versus PRP plus intravitreal ranibizumab for high-risk proliferative diabetic retinopathy. *Acta Ophthalmologica.* 2011;89:567-72.
17. Seo J, Park I. Intravitreal Bevacizumab for Treatment of Diabetic Macular Edema. *Korean J Ophthalmol.* 2009;23:17.
18. Özkiriş A. Intravitreal bevacizumab (Avastin) for primary treatment of diabetic macular oedema. *Eye* 2008;23:616-20.
19. Haritoglou C, Kook D, Neubauer A, Wolf A, Priglinger S, Strauss R, et al. Intravitreal Bevacizumab (avastin) therapy for persistent Diffuse Diabetic Macular Edema. *Retina.* 2006;26:999-1005.
20. Arevalo J, Sanchez J, Fromow-Guerra J, Wu L, Berrocal M, Farah M et al. Comparison of two doses of primary intravitreal bevacizumab (Avastin) for diffuse diabetic macular edema: results from the Pan-American Collaborative Retina Study Group (PACORES) at 12-month follow-up. *Graefes Arch Clin Exp Ophthalmol.* 2009;247:735-43.
21. Soheilian M, Ramezani A, Bijanzadeh B, Yaseri M, Ahmadi H, Dehghan M et al. Intravitreal Bevacizumab (avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of Diabetic Macular Edema. *Retina.* 2007;27:1187-95.
22. Jorge R, Costa RA, Calucci D, Cintra LP, Scott IU. Intravitreal bevacizumab (Avastin) for persistent new vessels in diabetic retinopathy (IBEPE study). *Retina* 2006; 26:1006-13.
23. Arevalo J, Wu L, Sanchez J, Maia M, Saravia M, Fernandez C et al. Intravitreal bevacizumab (avastin) for proliferative diabetic retinopathy: 6-months follow-up. *Eye.* 2007;23(1):117-23.
24. Minnella A, Savastano C, Ziccardi L, Scupola A, Sasso P, Falsini B et al. Intravitreal bevacizumab (Avastin®) in proliferative diabetic retinopathy. *Acta Ophthalmologica* 2008;86:683-7.
25. S Pillai G, Khake A, Pehera N, Nambyar R, Bhat L, Rao A et al. Intravitreal Bevacizumab in Diabetic Retinopathy. *Kerala J Ophthalmol.* 2015;11:266-9.
26. Baig MS, Rehman A, Burney JA. Intravitreal bevacizumab (Avastin) for proliferative diabetic retinopathy. *Pakistan J Sur.* 2009;25(2):110-4.

27. Jahangir T, Jahangir S, Tayyab H, Hamza U. To determine the effect of intravitreal bevacizumab (Avastin) on visual acuity in patients with persistent diabetic macular edema. *Pak J Ophthalmol.* 2011;27(4):187-90.
28. Kumar A, Sinha S. Intravitreal bevacizumab (Avastin) treatment of diffuse diabetic macular edema in an Indian population. *Indian J Ophthalmol.* 2007;55:451.
29. Ahmadieh H, Ramezani A, Shoeibi N, Bijanzadeh B, Tabatabaei A, Azarmina M et al. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. *Graefes Arch Clin Exp Ophthalmol.* 2007;246:483-89.
30. Lam D, Lai T, Lee V, Chan C, Liu D, Mohamed S et al. Efficacy of 1.25 mg versus 2.5 mg intravitreal bevacizumab for diabetic macular edema. *Retina.* 2009;29:292-9.

Cite this article as: Ankur, Kumar Y, Arora D, Tyagi R, Mittal SK. Fundus fluorescein angiographic assessment of patients with proliferative diabetic retinopathy and macular edema before and after intravitreal injection of Bevacizumab. *Int J Res Med Sci* 2019;7:4111-8.