Original Article

Resolution of Macular Oedema in Diabetic Patients Following Avastin (Bevacizumab) Intravitreal Therapy

Ata-ur-Rehman, Saba Alkhairy, Farnaz Siddiqui, Mirza Shafiq Ali Baig

Pak J Ophthalmol 2017, Vol. 33, No. 2

See end of article for authors affiliations

Correspondence to:
Ata ur Rehman
Dept of ophthalmology
Liaquat National Hospital
PECHS, Karachi
Email:
dr_ataurrehman@hotmail.com

Purpose: To estimate the effectiveness of intravitreal Avastin (bevacizumab) treatment in the reduction of macular oedema in diabetic patients.

Study Design: Prospective Cohort study.

Place Duration of study: **O**utpatient department (OPD) of the Ophthalmology department of Liaquat National Hospital (LNH) between the period April 2013 March 2015.

Material Methods: A total of 66 eyes of 44 patients (both type 1 type 2 diabetics) were selected who were advised their first intraocular Avastin in one or both eyes with clinically visible angiographically confirmed macular oedema and those who did not have a prior history of grid laser photocoagulation. All subjects were treated by intravitreal avastin (bevacizumab) 1.25 mg injection. Best-corrected visual acuity, slit lamp examination and fundus fluorescein angiography were examined before after intravitreal injection.

Results: A total of 66 eyes of 44 patients (both type I Type II diabetes) without any prior history of Avastin were included in the study. There were 26 (59%) males 18 (41%) females. The edema was seen completely resolved in 8 patients (12.2%), partially resolved 44 (66.7%) not resolved in 14 (21.21%). There was no adverse reaction seen in any eye except four eyes had mild anterior chamber inflammation which were treated with topical corticosteroid and one eye developed sub-conjunctival haemorrhage. The visual acuity improved in

59 out of 66 eyes (89%) based on the increased number of lines read by the patient on Snellen chart and in only 7 eyes there was no improvement during a mean follow-up period of 6 months.

Conclusion: Intravitreal bevacizumab injection provides significant improvement in visual acuity as well as reduction of macular oedema therefore may consider as a primary treatment of diabetic macular oedema.

Keywords: Anti-vascular endothelial growth factor; Bevacizumab; Diabetic macular edema; Diabetic retinopathy.

Diabetes mellitus can lead to diabetic retinopathy (DR) it is one of the commonest cause of blindness world wide[1,2]. Good glycemic control blood pressure control play an important role in the reduction of risk of development as well as progression of diabetic retinopathy. Proliferative diabetic retinopathy macular oedema are the most visually disabling complications of diabetic retinopathy[3,4,5]. Macular edema can develop at any stage of diabetic retinopathy it can lead to visual loss. Both proliferative non proliferative DR may show diabetic macular oedema (DME), which is classified as either focal, if edema is caused by a focal leakage from microaneurysms, or diffuse, if there is generalized leakage from retinal capillaries with abnormal permeability throughout the posterior pole[6,7,8].

Vascular endotheial growth factor (VEGF) leads to disruption in the blood retinal barrier increased vascular permeability which results in macular oedema therefore, anti-VEGF treatment inhibits the neovascularization diabetic macular oedema[9].

VEGF play an important role in the pathogenesis of diabetic retinopathy diabetic macular oedema, anti-VEGF agents are beneficial in the management of such conditions which have shown in multiple recent studies. It has been proved that intravitreal bevacizumab injection is inexpensive accessable in the management of diabetic macular oedema, it can be used along with laser photocoagulation. However, its clinical superiority compared with intravitreal ranibizumab other intravitreal Anti VEGF in terms of diabetic macular oedema regression the improvement of best corrected visual acuity are still unproven needs further analysis studies[10].

Bevacizumab (Avastin) is a humanized monoclonal antibody against VEGF it binds inhibits all the biologically active forms of VEGF. Bevacizumabis is a Food Drug Administration (FDA) approved treatment for metastatic colorectal cancer. It also showed beneficial effects in patients having choroidal neovascularization, iris neovascularization, vitreous haemorrhage macular oedema. However in persistent diffuse diabetic macular oedema there are only few studies that have shown the advantageous effects of intravitreal bevacizumab therapy[11.12].

The objectives of the study were 3 folds. To know the effectiveness of intravitreal Avastin treatment in the reduction of diabetic macular oedema. To gain information about the number of Avastin applications required to resolve DME in order to stabilize visual acuity (VA). To know the overall reduction in the rate of severe visual loss from DME both in the effectively

treated eyes in those eyes in which macular oedema was not resolved in spite of repeated injections.

MATERIALS METHODS

The study was performed simultaneously at the Ophthalmology department LNH and at the Eye Clinic between April 2009 – March 2015. This was a small prospective cohort study of 66 eyes of 44 diabetic patients of either sex age presented at the OPD and fulfilled the inclusion criteria.

Patients were selected from the Eye OPD presenting to the Hospital. All screened diabetic patients underwent visual acuity assessment using Snellens Chart, slit lamp biomicroscpy for fundus examination with 90D lens, fundus flourescein angiography and laboratory investigations to assess their glycemic control. **The s**election criteria included those patients of both genders of ages between 45 to 75 years that were known diabetics who had manifest macular edema both on slit-lamp examination and FFA. These patients had reasonably clear media, received intra-vitreal treatment for the first time in a particular eye without previous laser photocoagulation. The exclusion criteria included patients with presence of neovessels at disc, neovessels elsewhere ischemic maculopathy and those who had a history of previous laser photocoagulation.

Patients were further categorized into 3 groups. Group 1 consisted of individuals with best corrected visual acuity of 6/60 or less, Group 2 consisted of individuals with best corrected visual acuity of 6/36 or 6/24 while group 3 consisted of individuals with best corrected visual acuity of 6/18 or better.

Treatment Procedure included use of intravitreal Avastin, 1.25mg in 0.05 ml given to all patients on monthly basis for 3-6 months depending on the response of the drug. In bilateral cases injections were given 2-7 days apart. Moxifloxacin was started 1 day before injection and was continued for 3 days after the therapy. Acetazolamide 250 mg stat was also given. All patients were followed-up on the very next day, at 4 weeks then monthly for 6 months. They were instructed to report immediately for any untoward reaction which was already explained to them.

The data was entered and analyzed on IBM SPSS package version 21. Frequency and percentages were calculated for categorical variables like gender, best corrected visual acuity (BCVA) etc. The Kruskal-Wallisnon parametric test was used to compare the BCVA in different groups before and 3 months after Avastin. A P-value ≤ 0.05 was considered as statistically significant.

RESULTS

There were a total of 66 eyes of 44 patients all of whom were diabetic. There were 26 (59%) males and 18 females (41%). The best corrected visual acuity (BCVA) in the eye to be treated (pre Avastin BCVA) was 6/18 Visual Acuity in 12 eyes (18%), 6/24 in 30 eyes (46%), 6/36 in 14 eyes (21%), 6/60 in 8 eyes (12%) and 3/60 in 2eyes (03%) (table 1). All 66 eyes were divided into 3 groups based on pre-avastin BCVA. Group 1 consisted of 10 eyes in whom BCVA was 6/60 or less, Group 2 consists of 44 eyes in whom BCVA was 6/36-6/24 Group 3 consists of 12 eyes in whom BCVA was 6/18 or better (Table 2).

Table 1: Best Corrected VA of subjects before Avastin.

BCVA	Number of Eyes (n = 66, %)
6/18	12 (18.18)
6/24	30 (45.45)
6/36	14 (21.21)
6/60	8 (12.12)
3/60	2 (3.03)

Table 2: Groups of subjects according to BCVA.

Groups	Number of Eyes (n = 66, %)	BCVA
1	10 (15.15)	6/60 or less
2	44 (66.67)	6/36-6/24
3	12 (18.18)	6/18

In Group 1, after 3 months of Avastin treatment, BCVA improved from 6/60 or less to 6/9 in 2 eyes, 6/12-6/18 in 4 eyes, 6/24-6/36 in 2 eyes and there was no improvement in 2 eyes ($p < 0.005$). In Group 2, after 3 months of Avastin treatment, BCVA improved from 6/36 – 6/24 to 6/6 - 6/9 in 6 eyes, 6/12-6/18 in 24 eyes, 6/24 in 12 eyes and there was no improvement in 2 eyes ($p < 0.001$). In Group 3, after 3 months of Avastin treatment, BCVA improved from 6/18 to 6/9 in 3 eyes, 6/12 in 6 eyes and no improvement was observed in 3 eyes ($p = 0.01$) (table 3).

All 66 eyes received 3 injections each while 24 eyes received 3 additional injections (table 6). Effect of Avastin treatment on DME whether it was completely resolved or partially resolved or not resolved at all based on clinical examination, FFA investigation and on post Avastin BCVA assessment was studied. In 8 (12.12%) eyes edema was completely resolved, In 44 (66.67%) it was partially resolved and in 14 (21.12%) it was not resolved at all (table 4).

DISCUSSION

Diabetic eye disease is one of the commonest causes of blindness in Pakistan[13]. It occurs due to changes in tiny blood vessels of the retina.

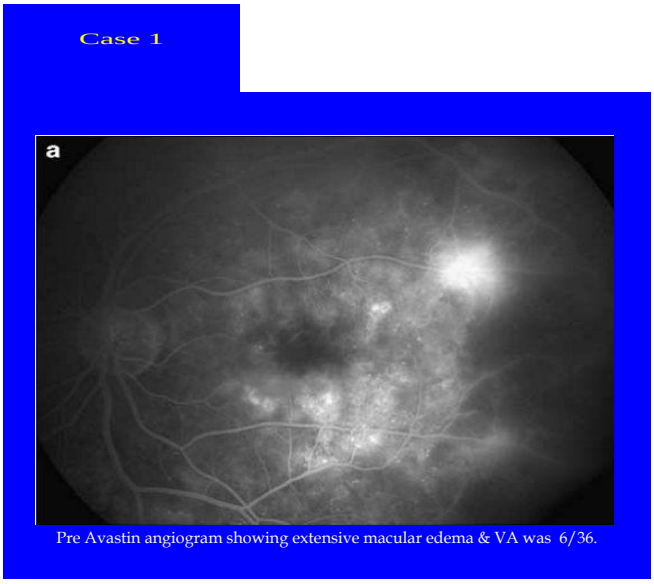
1. Visual impairment in diabetic patients is mostly caused by macular oedema as well as the disruption of inner blood-retinal barrier. DME results from a series of biochemical cellular

Table 3: Comparison of BCVA in groups before and 3 months after Avastin.

Groups	Pre-Avastin BCVA	3 months Post Avastin BCVA	P- Value
1	6/60 or less (n=10, 15.15%)	6/9 (n=2, 20%) 6/12-6/18 (n=4, 40%) 6/24-6/36 (n=2, 20%) No Improvement (n=2, 20%)	<0.005
2	6/36-6/24 (n=44, 66.67%)	6/6-6/9 (n=6, 13.64%) 6/12-6/18 (n=24, 54.55%) 6/24 (n=12, 27.27%) No improvement (n=2, 4.54%)	<0.001
3	6/18 (n=12, 18.18%)	6/6 (n=0, 0.0%) 6/9 (n=3, 25.0%) 6/12 (n=6, 50.0%) No improvement (n=3, 25.0%)	0.01

Table 4: Post Avastin Outcome on Oedema resolution.

Avastin Outcome	Number of Eyes (n = 66, %)
Edema completely resolved	8 (12.12)
Edema partially resolved	44 (66.67)
Edema not resolved	14 (21.21)



Pre Avastin angiogram showing extensive macular edema & VA was 6/36.

Post Avastin angiogram of the same patient, after 3 avastin applications VA improved to 6/6

changes, causing progressive leakage and exudation. Focal grid photocoagulation used to be the standard of care for diabetic maculopathy. However, the availability of new agents raises the possibility of improvements if significant benefits can be validated in randomized clinical trials[14]. Aozkir showed that intravitreal bevacizumab injection appears to be effective in the primary treatment of DME. In his study, 24 eyes showed an improvement in VA with a decrease in fluorescence in leakage on FFA which was consistent with our study[15]. Another study showed that with doses of 1.25 mg and 2.5 mg of Avastin as primary treatment of diabetic macular edema there was an anatomical functional improvement in 55.1% of eyes[16]. Still another study done by Kumar et al also showed an improvement in BCVA at 3 months with a significant decrease in macular thickness[17]. Another study by Khan et al showed the mean BCVA of 0.726 logMar was improved to 0.452 LogMar at the 3rd month after intravitreal Bevacizumab[18].

There are other anti VEGFs that are used in the treatment of diabetic macular edema like ranibizumab and aflibercept but Bevacizumab remains the best option, in terms of price and value over aflibercept and ranibizumab for treatment of diabetic macular edema[17].

A few side effects were observed in our patients. Although there were no systemic side effects. Four patients developed mild anterior chamber reaction and 1 patient developed sub-conjunctival hemorrhage. Another study quoted that side effects such as endophthalmitis, intraocular inflammation, retinal detachment, IOP rise, sub-conjunctival hemorrhage and systemic side effects such as myocardial infarction and stroke may even occur. Therefore close monitoring is advised of these patients who were treated with anti VEGF[18].

There were a few limitations in our study. First, the follow-up time was relatively short, but visual and anatomical responses were apparent during the follow-up time. Second, there is no control group in this study, but it can be argued that the enrolled eyes served as their own controls because the pre- and post-treatment VAs and oedema map values of the same patients were compared. Third, VA was measured on a Snellen chart as opposed to the more standardized accepted ETDRS chart. However, all eyes were tested with the same correction throughout the follow-up period.

CONCLUSION

From this small study of 44 diabetic patients in whom macular oedema was treated with Avastin without

supportive grid laser photocoagulation, it has been evident that primary intra-vitreal Avastin at doses of 1.25 mg seems to provide stability or improvement in VA and FFA in DME at 6 months. Intravitreal avastin injection provides remarkable improvement in visual acuity of diabetic patients and regression of macular oedema.

Author's Affiliation

Dr. Ata Ur Rehman
Assistant Professor
Department or Unit: Ophthalmology

Dr. Saba Alkhairy
Assistant Professor
Department or Unit: Ophthalmology

Dr. Farnaz Siddiqui
Assistant Professor
Department or Unit: Ophthalmology

Prof. Mirza Shafiq Ali Baig
Professor
Department or Unit: Ophthalmology

Role of Authors

Dr. Ata Ur Rehman
Study design, manuscript writing.

Dr. Saba Alkhairy
Manuscript revision.

Dr. Farnaz Siddiqui
Data collection.

Prof. Mirza Shafiq Ali Baig
Critical analysis.

REFERENCES

1. **Klein BE**. Overview of epidemiologic studies of diabetic retinopathy. Ophthalmic Epidemiol. 2007; 14: 179–183.
2. **Pascolini D, Mariotti SP.** Global estimates of visual impairment: 2010. Br J Ophthalmol. 2012; 96: 614–618.
3. **Nicholson BP, Schachat AP.** A review of clinical trials of anti-VEGF agents for diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2010; 248: 915–930.
4. **Klein R, Klein BE, Moss SE**. Visual impairment in diabetes. Ophthalmology. 1984; 91: 1–9.
5. **Soheilian M, Garfami KH, Ramezani A, Yaseri M, Peyman GA.** Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. Retina. 2012; 32: 314–321.
6. **Lang GE, Lang SJ**, Klinik und therapie des diabetis chenmakulaödems. Klinische Monatsblatterfür Augenheilkunde 2011; 228: 1–13.
7. **Lang GE.** Diabetic macular edema. Ophthalmologica. 2012; 27: 21–29.
8. **Stefanini FR, Arevalo JF, Maia M.** Bevacizumab for the management of diabetic macular edema, World Journal of Diabetes. 2013; 4: 19–26.
9. **Ozkiris A, Evereklioglu C, Oner A, Erkilic K**. Pattern electroretinogram for monitoring the efficacy of intravitreal triamcinolone injection in diabetic macular edema. *Doc Ophthalmol*. 2004; 109: 139-145.
10. **Ozkiris A, Evereklioglu C, Erkilic K, Tamcelik N, Mirza E**. Intravitreal triamcinolone acetonide injection as primary treatment for diabetic macular edema. *Eur J Ophthalmol*. 2004; 14: 543-549.
11. **Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L *et al*.** Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors other disorders. *Cancer Res.* 1997; 57: 4593-4599.
12. **Chen Y, Wiesmann C, Fuh G, Li B, Christinger HW, McKay P *et al*.** Selection analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. *J Mol Biol*. 1999; 293: 865-881.
13. **Shaikh A, Fahemullah S, Ziauddin A, Jamshed A.** Prevalence of Diabetic Retinopathy influence factors among newly diagnosed Diabetics in Rural Urban Areas of Pakistan. Pakistan journal of medical Science, 2008; 24: 6.
14. **Yannis M, Paulus Mark S, Blumenkranz, MD**. Panretinal Photocoagulation for Treatment of Proliferative Diabetic Retinopathy. American Academy of Ophthalmology 2013.
15. **Ozkirs A**. Intravitreal Bevacizumab (Avastin) for Primary Treatment of Diabetic Macular Oedema. The scientific journal of royal college of ophthalmologists. 2009; 23 (3): 616-620.
16. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, et et al. Primary Intravitreal Bevacizumab (Avastin) for diabetic macular edema. results from the Pan-American study group at 6 months follow up. Ophthalmology 2007; 114: 743-750.
17. **Kumar A, Sinah S.** Intravitreal Bevacizumab treatment of diffuse macular edema in an Indian population. Indian J ophthalmol. 2007; 55: 451-455.
18. **Khan A, Amir AC, Zahid C**. Intravitreal bevacizumab for treatment of diabetic macular edema. Pak J ophthalmol 2012; 28: 3-9.
19. **Deepak C.** Bevacizumab offers best value of anti-VEGF drugs to treat DME. Endocrinology news. 2016.
20. **Ghasemi K, Nguyen QD.** Adverse events complications associated with intravitreal injections of anti VEGF agents. Eye, 2013; 27: 787-794.