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DIABETIC MACULAR EDEMA;

ROLE OF INTRAVITREAL BEVACIZUMAB IN TREATING CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA

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ABSTRACT... OBJECTIVE: To evaluate the effect of Intravitreal Bevacuzimab on Best Corrected Visual Acuity in patients with clinically significant diabetic macular edema. **MATERIAL AND METHODS:** A prospective uncontrolled interventional case series in which 42 eyes of 31 consecutive diabetic patients with clinically significant macular edema and no significant comorbid ocular association presenting in the outpatients department of Holy Family Hospital and EYE SURGERY clinic, Rawalpindi Pakistan and opting for the treatment from 1st September 2013 to 31st January 2014 were given an intravitreal injection of Bevacizumab. BCVA was documented prior to and four weeks after the injection. Main outcome measure was changes in BCVA. **RESULTS:** Out of the 31 patients included in the study 14(45.16%) were male and 17 (54.83%) female. Average age was 56.1 ± 7.6. All 31 patients (42 eyes) came for follow up and their BCVA recorded. 41 (97.61%) eyes showed an improvement of one or more line on Snellen's chart at 4 weeks. 14 (33.33%) eyes showed an improvement of one line, 19 (45.23%) eyes an improvement of two lines, 6 (14.28%) eyes three lines and just 2 (4.76%) eyes had an improvement of four lines on Snellen's chart at 4 weeks. Only 1(2.38%) eye remained same with no worsening. On logMAR conversion scale for Snellen's letters the BCVA improved from 0.76 ± 0.27 to 0.47 ± 0.27 ($p < 0.001$). No significant complications were observed in any of the eyes. **CONCLUSION:** The use of intravitreal Bevacizumab (1.25mg/0.05ml) is a safe and effective moe of treatment for clinically significant diabetic macular edema.

Key words: Anti VEGF, Intravitreal Bevacizumab, Clinically significant diabetic macular edema, Best corrected visual acuity.

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INTRODUCTION

Diabetes is a Worldwide Epidemic. There are about 135 million people with diabetes worldwide (90% type 2) and almost 300 million people with diabetes projected by 2025. Prevalence of DR of any severity in the diabetic population is 30% and prevalence of blindness due to DR is approximately 5%[1]. Data from 2011 WHO statement suggests that in Pakistan the total prevalence of diabetes is 12.9 million (10% of total population).

Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision. Diabetic macular edema is caused by excessive vascular permeability, resulting in the leakage of fluid and plasma constituents, such as lipoproteins, into the retina, leading to its thickening. When this obeys certain clinical criteria it is known as clinically significant macular edema. Although visual loss secondary to proliferative changes is more common in patients with type 1 diabetes, visual loss in patients with type 2 diabetes is more commonly due to macular edema[2].

The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that laser photocoagulation is beneficial in the treatment of clinically significant macular edema. However, certain eyes with DME are resistant to conventional laser photo-coagulation[3].

Intravitreal Triamcinolone Acetonide (IVTA) injection has proven effective in improving vision and reducing macular thickness in DME, both as an initial treatment and as a second line therapy after unsuccessful laser therapy. However, its effect is temporary, and a number of side effects have been reported[4].

Vascular endothelial growth factor (VEGF) has been implicated as an important factor in the breakdown of the blood-retina barrier, with increased vascular permeability resulting in retinal edema in diabetic patients by affecting the endothelial tight junction proteins[5]. Therefore anti-VEGF treatments have been proposed as an alternative adjunctive treatment for DME[6].

Anti-VEGF agents like pegaptanib sodium and ranibizumab have been evaluated for DME in Phase II randomized trials and a pilot study respectively with fairly promising results[7,8].

Bevacizumab (Avastin, Genentech Inc., San Francisco, CA) is a complete full-length humanized antibody that compared to pegaptanib and ranibuzimab which are selective binders, inhibits all active isoforms of VEGF. It has been used successfully as a systemic drug in tumor therapy[9].

Recent studies have demonstrated the usefulness of an intravitreal injection of bevacizumab (IVB) in the reduction of macular edema secondary to central retinal vein occlusion, vascular permeability and fibrovascular proliferation in retinal neovascularization secondary to PDR, and choroidal neovascularization secondary to age-related macular degeneration (AMD)[10-12].

In our study we have tried to assess the usefulness of intravitreal Bevacuzimab in treating clinically significant diabetic macular edema by the level of improvement achieved in the best corrected visual acuity of our patients. Thereby, reducing the load visually handicapped dependant population in the society.

MATERIAL AND METHODS

Our study was a prospective uncontrolled interventional case series. 42 eyes of 31 consecutive diabetic patients with clinically significant macular edema presenting in the outpatients department of Holy Family Hospital and EYE SURGERY clinic, Rawalpindi Pakistan from 1st September 2013 to 31st January 2014, who after proper discussion and counseling opted for the offered treatment were included in the study. Patients with advanced diabetic eye disease including vitreous hemorrhage, marked fibrotic changes and tractional retinal detachment, other significant ocular conditions including cataract, glaucoma, age-related macular degeneration, and post-traumatic and non-diabetic vascular retinal pathologies were excluded from the study. Patients undergoing laser treatment or IVTA were also not included in the study sample.

After performing a detailed history and examination including best corrected visual acuity (BCVA), slit lamp examination with stereoscopic indirect biomicroscopy and IOP measurement, entries were made in a specially designed proforma. After taking proper consent an intravitreal dose of Bevacuzimab (Avastin) 1.25mg/0.05ml through a prefilled syringe (29 guage insulin syringe) from Shaukat Khanum Memorial Trust Hospital was injected to each patient. Proper sterilization and disinfection protocols were followed. The injection site was 3.5mm and 4mm from the limbus in psedophakic and phakic eyes, respectively. The needle was taken out after approximately 5 to 10 seconds and immediately a stick swab applied to the site for about 20 to 30 seconds to prevent any regurge. All the patients were followed after four (04) weeks. A complete examination was again performed. All the relevant findings were recorded into the proforma including the BCVA. The visual acuity was determined by a Snellen's chart and documented along with the logMAR conversion of Snellen's visual acuity. The main outcome measure was improvement in the BCVA in terms of number of lines improved on the Snellen's chart. All the findings were shown in terms of percentage

of patients (eyes) showing improvement. Also improvement in the mean of logMAR of Snellen's visual acuity was calculated and p value determined.

RESULTS:

Out of the 31 patients included in the study 14(45.16%) were male and 17 (54.83%) female. Average age was 56.1 ± 7.6. All 31 patients (42 eyes) came for follow up and their BCVA recorded. 41 (97.61%) eyes showed an improvement of one or more line on Snellen's chart at 4 weeks. 14 (33.33%) eyes showed an improvement of one line, 19 (45.23%) eyes an improvement of two lines, 6 (14.28%) eyes three lines and just 2 (4.76%) eyes had an improvement of four lines on Snellens chart at 4 weeks. Only 1(2.38%) eye remained same with no worsening. On logMAR conversion scale for Snellen's letters the BCVA improved from 0.76 ± 0.27 to 0.47 ± 0.27 ($p < 0.001$).

No significant complications were observed in any of the eyes. Only 7 (16.66%) eyes had a mild to moderate subconjunctival hemorrhage and 6 (14.28%) eyes had a mild regurge which in most cases is usually, predominantly the vitreous humour.

DISCUSSION:

Diabetic macular edema is the main cause of decreased central vision in patients with diabetic retinopathy. Its pathophysiology is explained by the loss of pericytes and breakdown of the inner blood retinal barrier resulting in increased vascular permeability[13].

Diabetic macular edema can be diffuse or localized. When it fits into the following criteria as defined in the ETDRS3 it is known as clinically significant macular edema.

- Retinal thickening within 500 μm of the center of the fovea.
- Hard, yellow exudates within 500 μm of the center of the fovea with associated retinal thickening (which maybe outside the 500 μm).
- At least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the center of the fovea.

The diagnosis is essentially clinical but Optical Coherence Tomography and fundus fluorescein angiography provide useful tools in documenting and provide useful adjunctive tools in the management of diabetic macular edema. However, due to lack of facilities we totally relied on the findings of the clinical examination. Therefore, we chose to follow a standard criteria in selecting our patients and instead of all the patients with diabetic macular edema only those with clinically significant macular edema were included in the study.

Various treatment modalities have been tried to overcome this condition. Intensive glycemic control[14] and blood pressure control[15], have some benefit.

The Early Treatment Diabetic Retinopathy Study (ETDRS) has shown that laser photocoagulation has significant benefit but is not always effective3. Similarly, intravitreal triamcinolone acetonide has shown some promise but has its own limitations with complications like raised IOP[4]. Other agents like oral protein kinase C[16] and intravitreal inserts of flucinolone acetonide[17] have also shown some benefit.

Vascular endothelial growth factor (VEGF) has been shown to be an endothelial cell-specific mitogen and an angiogenic inducer. Also known as vascular permeability factor, it has been demonstrated to increase retinal vascular permeability by increasing the phosphorylation of tight junction proteins. Hypoxia has been shown to be one of the major inducer of VEGF gene transcription[5].

This information has prompted the use of anti VEGF agents by various investigators in treating diabetic macular edema.

In a pilot study Chun et al reported that ranibizumab therapy has the potential to maintain or improve BCVA and reduce retinal thickness in

patients with DME[7]. In addition the Macugen Diabetic Retinopathy Study Group reported gains in VA of 10 letters in 34% and 15 letters in 18% of patients with DME after an intravitreal pegaptanib sodium injection in a randomized, double-masked, multicenter trial with a follow-up of 36 months[8].

Recently, the less costly intravitreal bevacizumab, a full length, humanized monoclonal antibody against VEGF, which binds and inhibits all the biologically active isoforms of VEGF-A, has been used to inhibit the release of VEGF and contribute to the integrity of the inner blood-retinal barrier, reduce extravasation from leaking blood vessels, and have beneficial effect in the prevention and treatment of macular oedema[18,19].

Haritoglou et al, in their report published about patients with persistent DME after photo-coagulation and intravitreal triamcinolone acetonide treatment. When treated with 1.25 mg intravitreal bevacizumab injection, the vision improved significantly from base line of 0.86 +log MAR to a value of 0.75 +log MAR at 6 weeks[20].

Arevalo et al[21] with their Pan-American Collaborative Retina Study Group in a retrospective study demonstrated the efficacy of 1.25 mg or 2.5 mg of intravitreal bevacizumab as primary treatment of DME, as 55.1% of eyes showed anatomical and functional improvement. In addition, they suggest a reduced risk of VA loss in 96.2% of eyes with DME treated with intravitreal bevacizumab.

Ozkiris A[22] presented results of 30 eyes, out of which 24 (80%) eyes showed increased visual acuity after mean, follow up time of 5.6 months after intravitreal bevacizumab injection. BCVA improved from 1.09±0.23 Log Mar (at baseline) to 0.90±0.17 Log Mar at 1st month.

Studies have also been conducted in Pakistan. Tareen et al[23] in their study at Al-Ibrahim Eye Hospital Karachi documented an improvement in BCVA from 0.42±0.14 Log Mar unit at base line to mean 0.34±0.13 Log Mar unit after one month of 1st intravitreal bevacizumab injection.

In another prospective interventional case series study carried out in Karachi, on 24 eyes to describe the effect of intravitreal bevacizumab on visual acuity and central macular thickness in patients with DME who were already treated with macular laser photocoagulation, the improvement in BCVA was found to be 0.90±0.22 (p=<0.001) at one month[24]. Khan et al[25] in their work demonstrated that 96.15% of their patients had an improvement of VA and macular edema resolved completely in 69.23% and moderately in 26.92% patients.

In our study BCVA improved from 0.76 ± 0.27 to 0.47 ± 0.27 with a very significant p value of < 0.001. The improvement ranges from a minimum of one line to upto four lines on the Snellen's visual acuity chart. 97.61% of the eyes in our study group showed an improvement in BCVA, whereas, the only eye which did not show any improvement at least remained stable with no further deterioration. These results match and are comparable with other contemporary international and national research work on this subject. None of our patients developed any complication apart from a mild subconjunctival hemorrhage in a few eyes specially those patients who were on antiplatelet therapy and had uncontrolled hypertension. Regurge from the injection site was sometimes encountered which was minimized and kept in control by displacing the conjunctiva slightly before the prick and applying a stick swab to the injection site immediately after the withdrawal of the needle. A quasi-experimental study conducted on 200 patients to assess the ocular complications after intra-vitreal Bevacizumab (Avastin) injection complications rate was only 12%. Most prominent complication was sub conjunctival hemorrhage (50)% followed by corneal abrasion in (16.7%). It was concluded that intravitreal Bevacizumab adverse effects were mostly procedure related[26]. The safety of intravitreal bevacizumab has also been confirmed by previous animal studies and human trials[27,28].

CONCLUSION:

Although our sample size was small and study duration short our results have demonstrated that intravitreal Bevacizumab is significantly effective in treating clinically significant diabetic macular edema. Although these were short term results they have provided us with a guideline and confidence to proceed to a longer duration study with a larger sample size. The use of intravitreal Bevacizumab (1.25mg/0.05ml) is a safe, effective and less costly mode of treatment for diabetic macular edema.

REFERENCES:

1. Zimmet P, Alberti KG, Shaw J. **Global and societal implications of the diabetes epidemic.** Nature 2001; 414:782–7.
2. Richter B, Kohner E. **Medical interventions for diabetic retinopathy. In: Wormald R, Smeeth L, Henshaw K, eds.** Evidence-Based Ophthalmology. London: BMJ Books; 2004:331–40.
3. **Early Treatment Diabetic Retinopathy Study Research Group. Treatment technique and clinical guidelines for photocoagulation of diabetic macular edema; Early Treatment Diabetic Retinopathy Study report No 2.** Ophthalmology. 1987;94:761-774.
4. Gillies MC, Sutter FK, Simppson JM, Simpson JM, Larsson J, Ali H, et al. **Itravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial.** Ophthalmology 2006; 113:1533-1538. doi:101016/j.ophtha.2006.02.065.
5. Ferrara N. **Vascular endothelial growth factor: basic science and clinical progress.** Endocr Rev 2004; 25:581–611.
6. Tolentino, MJ, Miller JW, Gragoudas ES. et al. **Intravitreous injections of vascular endothelial growth factor produce retinal ischemia and microangiopathy in an adult primate.** Ophthalmology 1996; 103: 1820–1828.
7. Chun DW, Heier JS, Topping TM, et al. **A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema.** Ophthalmology 2006; 113:1706–12.
8. **Macugen Diabetic Retinopathy Study Group. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema.** Ophthalmology 2005; 112:1747–57.
9. 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.
10. Spaide RF, Fisher YL. **Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage.** Retina 2006; 26:275–8.
11. Michels S, Rosenfeld PJ, Puliafito CA, et al. **Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration. Twelve-week results of an uncontrolled open-label clinical study.** Ophthalmology 2005; 112:1035–47.
12. Iturralde D, Spaide RF, Meyerle CB, et al. **Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: a short-term study.** Retina 2006; 26:279–84.
13. Ciulla TA, Amador AG, Zinman B. **Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies.** Diabetes Care 2003; 26: 2653-2664
14. **Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on development and progression of long-term complications in insulin dependent diabetes mellitus.** N Engl J Med. 1993; 329: 977-86.
15. UK Prospective Diabetes Study Group. **Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabete** UKPDS 38. BMJ. 1998; 317: 703-13.
16. Campochiaro PA, C99-PKC412-003 Study Group. **Reduction of diabetic macular edema by oral administration of the Protein Kinase C inhibitor PKC 412.** Invest Ophthalmol Vis Sci. 2004; 45:922-931. doi:10.1167/ivos.03-0955
17. Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Morono JR, et al. **Sustained delivery fluocinolone Acetonide vitreous inserts provide benefit for at least 3 years in patients with Diabetic macular edema.** Ophthalmology 2012; 119:2125-2132. doi:10.1016/j.ophtha.2012.04.030
18. Costa RA, Jorge R, Calucci D, Melo Jr LA, Cardillo JA, Scott I. **Intravitreal bevacizumab (avastin) for central and hemicentral retinal vein occlusions: IBeVO study.** Retina 2007; 27: 141-149.

19. Friedlander SM, Welch RM. **Vanishing disc neovascularization following intravitreal bevacizumab (avastin) injection.** Arch Ophthalmol 2006; 124: 1365.

20. Haritoglou C, Kook D, Neubauer A, et al. **Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema.** Retina. 2006; 26: 999–1005.

21. Arevalo JF, Fromow G, Quiroz MH, Sanchez JG, Wu L, Maia M, et al. **Pan- American collaborative Retina Study Group. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from Pan-American Collaborative Retina Study group at 24 months.** Ophthalmology 2009; 116:1488-1497. doi:10.1016/j.ophtha.2009. 03.016.

22. Ozkiris A. **Intravitrel bevacizumab (Avastin) for primary treatment of diabetic macular edema.** Eye. 2009;23:616-620. doi:10.1038/eye.2008.40.

23. Tareen IH, Rahman A, Mahar PS, Memon MS. **Primary effects of intravitreal bevacizumab in patients with diabetic macular edema.** Pak J Med Sci 2013; 29(4):1018-1022. doi: http://dx.doi.org/10.12669/pjms.294.3735

24. Shaikh FF, Arain AR. **Effect of intravitreal bevacizumab in diabetic macular edema.** Pak J Med Sci 2011; 27(3):651-655.

25. Khan A, Choudhry A A, Siddiq Z, Hussain M, Mubaruk B. **Intravitreal Bevacizumab for Treatment of Diabetic Macular Edema**. Pak J Ophthalmol 2012; 28(1): 3-9.

26. Khan A, Mahar PS, Hanfi AN, Qidwai U. **Ocular Complications after Intravitreal Bevacizumab Injection in Eyes with Choroidal and Retinal Neovascularization.** Pak J Ophthalmol 2010;26:205-209.

27. Feiner L, Barr EE, Shui YB, Holekamp NM, Brantley Jr MA. **Safety of intravitreal injection of bevacizumab in rabbit eyes.** Retina 2006; 26: 882-888.

28. Ziemssen F, Grisanti S, Bartz-Schmidt KU. **The international intravitreal bevacizumab safety survey.** Br J Ophthalmol 2006; 90: 1440-1441.