RESEARCH ARTICLE

Factors affecting the visual outcomes and central macular thickness in diabetic maculopathy after intravitreal bevacizumab

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Abstract

Objective: To assess the outcomes of intravitreal bevacizumab in patients of diabetic maculopathy by anatomical outcomes and best-corrected visual acuity, and to assess the prognostic factors that influence the efficacy of intravitreal bevacizumab.

Method: The quasi-experimental study was conducted at the Department of Ophthalmology, Fauji Foundation Hospital, Rawalpindi, Pakistan, from January 2019 to January 2020, and comprised patients with diabetic maculopathy who were administered intravitreal bevacizumab on a monthly basis for three months with further injections administered on an as-needed basis in cases of persistent macular oedema or deterioration of best-corrected visual acuity. The assessment was done pre-injection, and three and six months after the injection. Outcome variables were best-corrected visual acuity and central macular thickness. Data was analysed using SPSS 22.

Results: Of the 34 patients, 2(5.9%) were males and 32(94.1%) were females. The overall mean age was 58±10 years. Of the 55 eyes, 27(49.1%) were right and 28(50.9%) were left eyes. After 3 months, the best-corrected visual acuity improved by one line in 20(36.4%) eyes. At 6 months, it improved by one line in 25(45.4%) eyes. After 3 months, the central macular thickness of 48(87.2%) eyes improved anatomically. At 6 months, a further decrease in central macular thickness resulted in 50(90.9%) eyes. The best-corrected visual acuity at 6 months was inversely correlated with central macular thickness and disruption of inner segment/outer segment integrity.

Conclusion: Intravitreal bevacizumab injection led to appreciable improvement in best-corrected visual acuity and central macular thickness at 6 months. Disruption of inner segment/outer segment integrity, presence of exudates and cystic changes were noted that lead to poor visual prognosis.

Keywords: Intravitreal injection, Bevacizumab, Prognostic factors, Diabetic retinopathy, Optical coherence tomography.

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Introduction

Diabetes is a leading health threat in the developing world. It is estimated that by 2030, 10.2% (578 million) of the world's population will be affected by diabetes with a current incidence rate of 9.3% (463 million).[1] The prevalence of diabetes is higher in low and middle-income countries (LMICs) like Pakistan.[2] Diabetes is a systemic disease and is a precursor to blindness, renal diseases, coronary diseases, stroke and can lead to limb amputations. Complications from these and related illnesses are a major cause for concern and adversely affect the quality of life of individuals. At the societal level, the collective health cost associated with diabetes is alarming. Diabetes is surely one of the challenges of the 21st century.[3]

Diabetic retinopathy is a leading cause of blindness in the 20-74 age group.[4] The principal causes of decreased vision in diabetics are macular oedema and macular ischaemia. Early diagnosis and prompt treatment can lead to enhanced quality of life and can restrict the illnesses from threatening severe loss of vision. The standard protocol for treating diabetic macular oedema (DME) relies on administering anti- vascular endothelial growth factor (VEGF), steroids as well as laser therapy, or combination therapy.[5] DME may occur at any stage of diabetic retinopathy either proliferative or non-proliferative and it can be diffuse or focal macular oedema. Currently, administration of anti-VEGF agents is one of the most promising approaches for the treatment of vision loss due to DME.[6] This is because VEGFs are known to contribute to hyperpermeability of retinal vessels which in turn causes DME.[7]

While literature supports the view that bevacizumab is effective in improving best-corrected visual acuity (BCVA)[5,8] many patients have not shown improvement in visual acuity (VA) despite receiving several injections. There is a need to investigate the reasons why VA is not improving despite monthly bevacizumab injections. It is interesting to see the correlations of bevacizumab efficacy with baseline BCVA, presence or absence of exudates, epiretinal membrane, cystic changes and presence of inner segment/outer segment (IS/OS) disruption in the patients. The current study was planned to assess the outcomes of

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intravitreal bevacizumab (IVB) in patients of diabetic maculopathy by anatomical outcomes and BCVA, and to assess the prognostic factors that influence the efficacy of IVB.

Patients and Methods

The quasi-experimental study was conducted at the Department of Ophthalmology, Fauji Foundation Hospital, Rawalpindi, Pakistan, from January 2019 to January 2020. After approval from the institutional ethics review committee, the sample size was estimated with significance level 5%, baseline central subfield thickness (CST) 401±98 µm[7] and CST at 3 months 276±88 µm.[7]

The sample was raised using non-probability purposive sampling technique. Those included were patients of either gender aged 25-70 years who presented with diabetic retinopathy and had DME. DME was defined as retinal oedema or exudates lying within 500 microns of the centre of the fovea, or retinal oedema of one-disc diameter any part of which was within one-disc diameter of the centre of the fovea. Eyes having central macular thickness (CMT) of more than 300 microns measured by spectral-domain optical coherence tomography (OCT) were included. Eyes having any other macular pathology other than diabetic retinopathy, eyes previously treated with panretinal-photocoagulation or macular grid within the preceding six months, presence of vitreomacular traction or patients with a history of stroke, bleeding disorders or pregnancy were excluded.

Data was collected after taking written informed consent from the patinets. Age, gender, duration of diabetes, previous history regarding retinopathy, hospital registration number and contact numbers were noted. A baseline ocular examination was done. BCVA was assessed using Snellen visual acuity chart. OCT was done at least one week before IVB. Pupils of both eyes were dilated using tropicamide eye drops. A retinal evaluation was done using the 20 diopters (D) lens with an indirect ophthalmoscope and with 90 D lens by the same consultant ophthalmologist. IVB 1.25mg in 0.05ml was given 3.5mm away from the limbus in pseudophakic and 4mm away from the limbus in phakic eyes under topical anaesthesia. Two further intravitreal injections were administered, once a month. Follow-up to see BCVA and OCT was done at 3 and 6 months with further injections administered on an as-needed basis in cases of persistent macular oedema or deterioration of BCVA. One-line improvement of BCVA from the baseline was defined as an improvement and BCVA was converted to decimal acuity (DA) for analysis. A decrease in CMT of about 10% was defined as a significant improvement from an anatomical point of view. The presence of hard exudates on the fovea, epiretinal membrane, cystic changes, IS/OS integrity in OCT and lens status of the patient were noted. Also noted were IVB complications.

Data was analysed using SPSS 22. Descriptive statistics were calculated for quantitative variables and were expressed as mean and standard deviation. Frequencies and percentages were calculated for qualitative variables. P<0.05 was considered statistically significant.

Results

Of the 34 patients, 2(5.9%) were males and 32(94.1%) were females. The overall mean age was 58±10 years. Of the 55 eyes, 27(49.1%) were right and 28(50.9%) were left eyes. On initial examination, there were 24(70.6%) hypertensive patients, 16(47%) had hyperlipidaemia, 12(35.2%) were anaemic, and 1(2.9%) was a smoker, with several of these comorbidities also existing simultaneously. The mean glycated haemoglobin (HbA1c) was 7.815±1.724. BCVA and CMT at presentation, 3rd and 6th months were noted (Table 1).

At presentation, VA and CMT were negatively correlated (r=-0.352, p<0.001). Among ocular prognostic factors, exudates on the fovea were present in 34(61.8%) eyes, while cystic changes in the fovea were present in 44(80%). The integrity of IS/OS was disrupted in 24(43.6%) eyes. There were no epiretinal membranes present. Intraocular pressure (IOP) >20 mmHg was present in 9(16.3%) eyes.

At the 3rd month, BCVA improved by one line in 20(36.4%) eyes, by two lines in 7(12.7%), and by three lines in 1(1.8%) eye, bringing total improvement in 28(50.9%) eyes. At the 3rd month, BCVA and CMT were inversely correlated (r=-0.539, p<0.01). At 6 months, compared to the baseline, BCVA improved by one line in 25(45.4%) eyes, by two lines in 10(18.2%) eyes, and by three lines in 3(5.4%) eyes, bringing total improvement in 38(69.1%) eyes, whereas it

Table-1: BCVA and CMT frequencies.

BCVA	**Presentation**(n)	**3rd month**(n)	**6th month**(n)
6/6	0	1	1
6/9	4	11	15
6/12	11	11	11
6/18	13	9	10
6/24	4	11	7
6/36	13	7	7
6/60	10	5	4
CMT (um)			
201-300	0	35	36
301-400	39	13	14
401-500	10	4	2
501-600	2	2	2
601-700	4	1	1

BCVA: Best corrected visual acuity, CMT: Central macular thickness, n: Number of eyes.

Table-2: Improvement in ocular parameters.

Best corrected Visual acuity (BCVA)				Central macular thickness (CMT)			
3rd month		6th month		3rd month		6th month	
	n (%)		n (%)		n (%)		n (%)
1 line	20 (36.4)	1 line	25 (45.4)	By 10%	48 (87.2)	By 10%	50 (90.9)
≥2 lines	8 (14.5)	≥2 lines	13 (23.6)				
Total	28 (50.9)	Total	38 (69.1)				

Table-3: Prognostic factors and their correlation with 6-month VA and CMT.

Prognostic factors		n (%)	Spearman's Correlation (r) with decimal VA		Spearman's Correlation (r) with CMT	
Stage of diabetic retinopathy	Mild NPDR with DME	8 (14.5)	*r*=-0.127	*p*=0.357	*r*= 0.316	*p*=0.019
	Moderate NPDR with DME	16 (29)				
	Severe NPDR with DME	23 (41.8)				
	PDR with DME	8 (14.5)				
Hypertension		24 (70.6)	*r*=0.155	*p*=0.257	*r*=-0.14	*p*=0.308
Hyperlipidaemia		16 (47)	*r*=-0.153	*p*=0.264	*r*=0.215	*p*=0.115
Nephropathy		12(35.2)	*r*=-0.168	*p*=0.219	*r*=0.164	*p*=0.232
Smoker		1(2.9)	*r*=0.166	*p*=0.226	*r*=-0.137	*p*=0.318
Anaemia		12 (35.2)	*r*=-0.058	*p*=0.673	*r*=0.117	*p*=0.397
Foveal exudates		34(61.8)	*r*=-0.414	*p*=0.002	*r*=0.323	*p*<0.016
Cystic changes on fovea		44(80)	*r*=-0.289	*p*=0.032	*r*=0.258	*p*=0.057
IS/OS disrupted		24(43.6)	*r*=-0.581	*p*<0.001	*r*=0.691	*p*<0.001

VA: Visual acuity (decimal acuity), CMT: Central macular thickness, NPDR: Non-proliferative diabetic retinopathy, DME: Diabetic macular oedema, PDR: Proliferative diabetic retinopathy, IS/OS: Inner segment/outer segment.

decreased in 2(3.6%) eyes of the same individual by one line each, and 15(27.3%) eyes showed no change in BCVA.

At the 3rd month, 48(87.27%) eyes had improved anatomically. At the 6th month, a further decrease in CMT from the 3rd month was seen in 2(3.6%) eyes. At 6 months, only 3(5.5%) eyes had worsened CMT values, 1(1.82%) showed no change, 1(1.82%) had decreased CMT but was not significant ($p>0.05$), while the rest had decreased CMT values compared to presentation, of which 50(90.9%) eyes had significantly reduced CMT (Table 2).

BCVA at 6 months was inversely correlated with CMT ($r=-0.755$, $p<0.001$) and disruption of IS/OS integrity on OCT ($r=-0.581$, $p<0.001$). It was positively associated with the absence of exudates on the fovea ($r=0.414$, $p=0.002$), absence of cystic changes on the fovea ($r=0.289$, p=0.032) and a higher presenting BCVA ($r=0.796$, $p<0.001$). Six-month CMT values were positively correlated with IS/OS disruption ($r=0.691$, $p<0.001$) and presence of exudates on the fovea ($r=0.323$, $p=0.016$). HbA1c was associated with progressive stages of diabetes ($r=0.380$, $p=0.004$). In other words, raised levels of Hba1c were linked to more advanced stage of the diabetic retinopathy. Finally, the decrease in CMT from the 3rd to the 6th month was positively associated with intact IS/OS integrity ($r=0.287$, $p=0.034$), and the decrease of CMT at 6 months compared to presentation was associated with the absence of cystic changes in the fovea ($r=0.268$, p=0.048). Prognostic factors and their correlation with six-month VA and CMT were noted (Table 3).

Discussion

Since the introduction of anti-VEGF therapy, it has become the treatment of choice for DME and has largely replaced laser. It not only reduces oedema and prevents further visual loss, but also results in improvement of BCVA, which was less common with laser. These days, anti-VEGF agents are used as the first port of call while treating centre-involving DME.[8,9]

The current study found that IVB injection given monthly for three months and then on an as-needed basis led to one or more than one-line improvement of BCVA in 50.9% of eyes at three months compared to baseline with further improvement witnessed at the six-month mark (69.1%). Furthermore, at 6 months, only 2(3.6%) eyes of the same individual showed degraded BCVA, with the remaining staying stable. Results reported in literature vary with regards to the efficacy of IVB concerning improvement in BCVA. For instance, Kumluang et al. reported that BCVA of only 47% eyes improved post-treatment, whereas Masih et al. report a figure of 73.33%.[10,11]

The improvement in CMT by 10% from baseline on OCT was seen in 87.2% and 90.9% eyes at 3 and 6 months, respectively. At presentation, CMT and VA were inversely related and also in the 3rd month VA and CMT were inversely correlated. VA at 6 months was inversely correlated with CMT. This statistical correlation is expected and is consistent with earlier findings.[12-14]

The current study noted a positive correlation between VA at 6 months and a higher presenting VA. Also noted was a trend that good BCVA at presentation led to less visual gain compared to worse vision at presentation. This trend was more marked in the 6th month compared to the 3rd month ($p=0.62$). Studies have shown that eyes with poor BCVA before treatment are more likely to experience larger gains in VA, perhaps because there is more room for improvement.[7,15]

Despite the excellent results achieved after treatment with intravitreal anti-VEGF agents, there are still some eyes that show incomplete responses to treatment.[16,17]

The present study noticed that the presence of IS/OS

disruption, hard exudates and cystic changes at fovea were associated with a poor outcome. Systemic factors, like hypertension, hyperlipidaemia, nephropathy and anaemia, did not show a correlation with BCVA post-treatment.

The current study showed that the presence of cystic changes at the macula was associated with a poor visual outcome. Macular cyst formation is known to cause ischaemia in DME. Yalcin et al. noted an increased possibility of macular ischaemia with increasing diameter of cysts, increased CMT and outer retinal layer damage.[18] Additionally, cystoid spaces in the outer plexiform layer were accompanied by photoreceptor damage beneath the cystoid spaces in eyes with DME.[19]

The current study also noted that the decrease of CMT from the 3rd to the 6th month was associated positively with an absence of cystic changes. Consistent with these findings, Sophie et al. noted that larger cystoid spaces were more detrimental to BCVA than the smaller ones.[20]

The present study noted a positive correlation between BCVA at 6 months and an absence of hard exudates at the fovea. The literature is not definitive on the correlation between hard exudates and BCVA.[7,21]

In the current study, BCVA at 6 months was inversely correlated with disruption of IS/OS integrity on OCT. The disturbance of the IS/OS junction, also known as the Ellipsoid zone (EZ), is known to reflect anatomical disruptions of the photoreceptors.[22] Several studies agree with the finding that damage of the IS/OS junction leads to poor visual prognosis.[23,24] In particular, Muftuoglu et al. showed that patients with shorter duration of DME and a lower baseline IS/OS damage were more likely to recover with an intact IS/OS.[24]

The current study has limitations, like a small sample size and short study duration.

More population-based prospective studies on a larger scale are required to explore the subject further.

Conclusion

IVB injection led to significant improvement in BCVA and CMT at six months. Disruption of IS/OS junction on OCT, presence of exudates, and cystic changes on OCT led to poor visual prognosis.

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