· Original article ·

Patient satisfaction and visual acuity after intravitreal bevacizumab as a treatment for macular edema in proliferative diabetic retinopathy

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Received:2009-06-01 Accepted:2009-08-18

Abstract

• AIM: To investigate patient assessed visual function and visual acuity after treatment with the unselective anti-VEGF inhibitor bevacizumab in diabetic macular edema after scatter laser photocoagulation due to proliferative diabetic retinopathy(PDR).

• METHODS: The case series of consecutive 30 eyes of 30 patients with PDR and persistent diabetic macular edema were treated with a single intravitreal dose of 1.25mg bevacizumab in 0.05mL (Avastin) in combination with scatter argon laser photocoagulation. The control group consisted of 30 eyes of 30 patients with PDR who received scatter laser photocoagulation alone. Main outcome measures were Snellen visual acuity, fundus clinical findings and patients self estimated quality of vision evaluated in scale of 0-100 percentages.

• RESULTS: Baseline visual acuity was mean 0.48±0.58 logMAR in the bevacizumab group and 0.61±0.78 (n.s.) in the control group. After 6 months, visual acuity hat not changed significantly to 0.33±0.41 and 0.52±0.68 in the bevacizumab and control group, respectively. Clinical examination showed only a trend to some improvement in macular edema. Subjective patient assessment of visual function on the visual analogue scale (VAS) showed an improvement from 60.2±17.5 to 76.0±15.6 ($P<0.01$) 6 months after the injection of bevacizumab. In the control group self-assessed visual function was mean 59.6±19.8, which did not differ from the baseline bevacizumab group (n.s.) but was high significantly ($P<0.01$) lower than after bevacizumab.

• CONCLUSION: Self-assessed visual acuity and patient satisfaction were significantly improved after intravitreal bevacizumab (Avastin) as additional therapy to scatter laser photocoagulation therapy for macular edema in PDR than after laser therapy alone. Visual acuity did not change significantly in this comparative case series over 6 months.

• KEYWORDS: proliferative diabetic retinopathy; visual acuity; self assessment; bevacizumab; scatter laser photocoagulation
DOI:10.3969/j.issn.1672-5123.2009.09.003

Ceklic L, Latinovic S, Neubauer AS, Malesevic M. Patient satisfaction and visual acuity after intravitreal bevacizumab as a treatment for macular edema in proliferative diabetic retinopathy. *Int J Ophthalmol (Guoji Yanke Zazhi)* 2009;9(9):1648-1651

INTRODUCTION

Diabetic retinopathy is a leading cause of visual impairment and blindness in developed countries and is the most common cause of blindness among people in working age[1]. It is a vision threatening disease which is, amongst others, characterized by microvascular changes starting with basement membrane thickening[2] and in later stages retinal vascular leakage and nonperfusion[3], mediated by numerous growth factors such as vascular endothelial growth factor (VEGF)[4]. The up-regulation of VEGF is associated with a breakdown of the blood-retinal barrier with increased vascular permeability resulting in retinal edema[5], stimulation of endothelial cell growth and neovascularisation, which can be prevented and reversed via VEGF inhibition in models[6]. In many studies unselective anti-VEGF inhibition by bevacizumab (Avastin) has been used recently for the treatment of diabetic macular edema[7-10]. There is, however, conflicting information on the increase in visual acuity obtained, which most likely is due to different patient populations investigated. While imaging techniques such as high-resolution optical coherence tomography (OCT) may help to elucidate those subgroups benefiting most from treatment, it should be kept in mind that patient experienced visual function is finally the patient relevant outcome. The patients' subjective visual performance is determined by different factors including not only visual acuity but also others such as visual fields, color vision, etc[11]. Therefore goal of the current study was to investigate patient assessed visual function and visual acuity after treatment with the unselective anti-VEGF inhibitor bevacizumab in diabetic macular edema after proliferative diabetic retinopathy (PDR).

MATERIALS AND METHODS

Materials We included patients with PDR and persistent diabetic macular edema who had received full-scatter argon

laser treatment at least three months prior to our intravitreal injection. A control group was defined by patients who received only full-scatter laser treatment without any additional treatment. All patients had clinically significant macular edema as defined by the ETDRS[12,13]. All cases included in the study in addition had some degree of NVEs or hemorrhages. Cases with vitreous hemorrhage, tractional retinal detachment, neovascular glaucoma or age related macular degeneration were excluded. We tried to minimize confounding by selecting patients who did not have eye treatments for at least the last three months and that had relatively good glucoregulation and controlled blood pressure. All patients underwent a full ophthalmologic exam by an experienced retinal specialist (L. C., S. L.) by stereoscopic fundus examination. Diabetic retinopathy and diabetic macular edema were graded in accordance with the American Academy of Ophthalmology recommendations[14].

Methods

The study was designed as a prospective, consecutive case series The total number of 30 individuals (19 male and 11 female) were included in the injection group of our study. Mean age of the patients was 51. 9 ± 9. 2 years, average duration of diabetes mellitus was 8. 1 ± 2. 3 years and HbA1C values was 6. 0% ± 4. 5%. All the patients had sufficient regulation of blood pressure, most (77%) medically controlled. In our control group of 30 patients (13 female and 17 male) with PDR but no intravitreal anti-VEGF, IDDM was in 21 (70%) and NIDDM was in 9 (30%) patients. Mean age of these individuals was 63. 2 ± 11. 1 years. Metabolic and blood pressure control was comparable. Intraocular pressure was and remained in a normal range without any medication in both groups (Table 1).

Macular edema was in 14 (47%) severity stage III, 12 patients (40%) stage II and only 4 patients (13%) had mild macular edema (stage I) in the treated group. This tended to some degree be more advanced edema than in the control group, where stage I with 12 patients (40%) was more prevalent and only 4 patients were in stage III. Baseline visual acuity was mean 0. 48 ± 0. 58 logMAR in the bevacizumab group and 0. 61 ± 0. 78 (n. s.) in the control group.

Follow up examinations were 1 month and 6 months after the injection or inclusion date. The exams included Snellen visual acuity, intraocular pressure (IOP) and fundus examination. At each visit the patients assessed their subjective quality of vision on a visual analogue scale (VAS), yielding values from 0 to 100, with 100 being best possible vision. This VAS is a well-established instrument e. g. in pain assessment[15] and also in quality of life assessments such as the EQ-5D[14]. Moreover, patient's satisfaction was asked on a simple 3 step scale as better, same or worse. Data were analyzed using SPSS for Windows and for all statistical tests, $P < 0.05$ was considered significant. All research was done in concordance with institutional guidelines and ethic committee consent and all patients provided written informed consent.

Injection technique Under sterile conditions of the operating room, topical anesthesia was induced by applying 10g/L tetracaine eye drops at least three times. Povidone-iodine (Betadine) was applied to the eyelid margins and the lashes, and conjunctival fornices. After application of a sterile drape and an eyelid speculum, intravitreal injection of 0. 05 mL volume containing 1. 25 mg of bevacizumab (Avastin, La Roche) using sharp 27-gague needle, has been applied unilaterally through the pars plana region of the bulbar, 4mm inferotemporal to the limbus. Combined antibiotic and steroide eye drops were applied 3 times a day for the next 4 days.

Table 1 Patients data and average logMAR VA

	Intravitreal Bevacizumab group	Control group
Gender: Male	19	17
Female	11	13
Age (y/r)	51. 9 ± 9. 2	63. 3 ± 11. 1
Type of diabetes: IDDM	19	26
NIDDM	11	4
Hemoglobin A1c	6. 0% ± 4. 5%	6. 5% ± 3. 3%
Blood pressure (mmHg)	131. 2 ± 7. 5	129. 5 ± 8. 1
	81. 4 ± 4. 5	80. 0 ± 5. 6
Intraocular pressure (IOP) (mmHg):	14. 0 ± 4. 6	13. 8 ± 4. 6
Baseline		
after 4wk	15. 0 ± 4. 1	14. 6 ± 3. 8
after 6mo	14. 6 ± 4. 1	14. 6 ± 4. 1
Visual acuity (VA): Baseline	0. 48 ± 0. 58	0. 61 ± 0. 78
4 weeks follow-up	0. 36 ± 0. 46	0. 55 ± 0. 65
6 months follow-up	0. 33 ± 0. 41	0. 52 ± 0. 68

RESULTS

While the control group shows no significant increase in visual acuity, the bevacizumab group shows a trend towards increased visual acuity, which is not statistically significant. Also, no group differences between the treated and untreated patients with macular edema after PDR laser treatment existed at any time investigated.

Patient assessment of visual function on the VAS increased from 60. 2 ± 17. 5 to 76. 0 ± 15. 6 ($P < 0.001$). Also, after 6 months the control group assessed their visual function mean 59. 6 ± 19. 8, which did not differ from the baseline bevacizumab group (n. s.) but was high significantly ($P < 0.01$) different from the bevacizumab group after 6 months. Six months after treatment, in the bevacizumab group, 15 patients (50%) graded their quality of vision with a score between 81%-100%, while this was the case in only 2 control group patients (7%, Figure 1). Most of control goup patients, 17 patients (57%), graded their quality of vision between 41%-60%, while the group 61%-80% was similar for both groups. Visual acuity correlated with the severity of diabetic macular edema in both groups prior to the intravitreal application of bevacizumab (Pearson correlation 0. 74, $P < 0.01$). At the six month follow-up correlation between visual acuity and severity of diabetic macular edema became insignificant (0. 27, $P < 0.01$) in the bevacizumab group. On clinical evaluation the diabetic macular edema showed some stabilisation and partial resolution six months after intravitreal injection, but those data were statistically non significant.

Most of the patients (24 individuals, 80%), reported better and 4 patients (13%) the same visual acuity (Figure 2). In

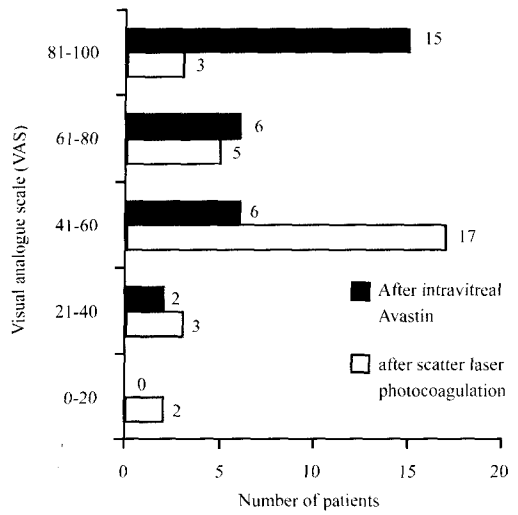

Figure 1 Self-assessed quality of vision 6 months after intravitreal bevacizumab

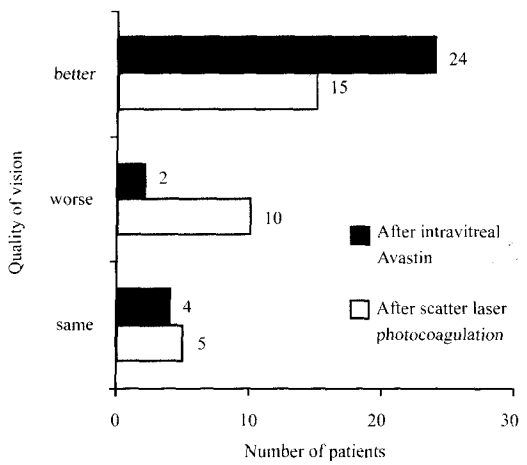

Figure 2 Patient satisfaction with quality of vision 6 months after treatments

the control group 15 patients (50%) reported better and 5 patients (17%) same visual acuity as before. Complications by the intravitreal bevacizumab injection occurred only in one case: a young diabetic woman developed intravitreal hemorrage two months after injection due to shrinkage of vitreoretinal proliferation from the optic disc. She later underwent vitrectomy. In all other patients no side effects of treatment were observed. Also, we did not record new neovascularisation or progression in diabetic retinopathy.

DISCUSSION

This study investigated the effect of intravitreal bevacizumab (Avastin) in patients with PDR and consecutive diabetic macular edema. While visual acuity did not improve significantly and clinical examination showed only a trend, subjective patient assessment could show a positive effect after 6 months follow-up. As macular diabetic edema is multifactorial disease, we hypothesised that the combination of selected therapeutic options, here laser photocoagulation and intravitreal bevacizumab could have better effect on visual outcome. Anti-VEGF therapy has been reccomended as a therapeutic option in diabetic retinopathy recently by several groups[7-9,16-21] and it could even have a positive effect on peripheral retinal ischemia which is a serious vision threatening complication in PDR[20]. On the other hand as the half-life of bevacizumab in aqueous humor is up to 4.32 days, and concentrations >10g/mL are maintained in the vitreous humor for 30 days[22,23], therefore it should be taken into consideration for multiple aplications. In the current study, only one injection had been performed, which might therefore underestimate effects.

Patient's visual acuity satisfaction and self assessed quality of vision after intravitreal injection showed a clear benefit-after 6 months and only one injection. This is important as it is well known, that visual acuity has a high influence on functional limitations in daily life activities[24]. A person who is visually disabled is even more likely to suffer from depression and mood disorders[25].

Impairment of vision is known to be associated with significant decrease in several areas of quality of life[26]. Better satisfaction and visual acuity assessment of PDR patients after intravitreal intervention was be correlated to the effect and objective stabilization and resolution of macular edema. Also, there is the difference between self assessed quality of vision estimated with VAS and quantitative description of quality of vision. It could be explained that some of the patients overestimated their visual acuity and under estimated their quality of vision. There was no statistically significant change in visual acuity, but a trend to improvement. As it is well known that after panretinal laser photocoagulation in PDR patients may have a discrete impairment in visual acuity [26], this finding appears clinically meaningful. Given the non-significant visual acuity trend one may hypothesize how bevacizumab contributes to the subjectively improved visual acuity assessment. This may for instance, occur by visual field improvements such as by reduction of macular thickness or even by stabilizing retinal perfusion.

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玻璃体腔注射贝伐单抗治疗 PDR 黄斑水肿后患者的满意度和视力

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摘要

目的:增生性糖尿病性视网膜病播散性视网膜激光光凝后,用非选择性抗 VEGF 抑制剂贝伐单抗治疗糖尿病性黄斑水肿,调查患者自我评估的视功能及视力。

方法:30 例 30 眼增生性糖尿病性视网膜病伴持续性糖尿病性黄斑水肿连续病例,播散性视网膜激光光凝后,1.25mg 贝伐单抗 0.05mL (Avastin)单剂量玻璃体腔注射治疗。对照组包括 30 例 30 眼增生性糖尿病性视网膜病,只接受播散性视网膜激光光凝。主要的调查结果包括 Snellen 视力,眼底临床检查和患者自我用 0-100 分数值范围评价的视觉质量。

结果:贝伐单抗组的平均基线视力为 0.48±0.58 logMAR,对照组为 0.61±0.78 (两组无显著差异)。6mo 后,视力没有显著的变化,贝伐单抗组和对照组分别为 0.33±0.41 和 0.52±0.68。临床检查显示黄斑水肿仅有一些改善趋势。患者用直观模拟标度尺主观评价视功能结果显示注射贝伐单抗 6mo 后由 60.2±17.5 改善至 76.0±15.6 ($P<0.001$)。对照组自我评估视功能平均值为 59.6±19.8,与贝伐单抗组基线值无显著差异,但是低于注射贝伐单抗后分数,差异有高度显著性($P<0.01$)。

结论:治疗增生性糖尿病性视网膜病的黄斑水肿,贝伐单抗(Avastin)玻璃体腔注射作为播散性激光光凝的辅助治疗较单纯的激光治疗后患者满意度和自我评价的视力显著改善。患者视力在 6mo 后无明显变化。

关键词:增生性糖尿病性视网膜病;视力;自我评估;贝伐单抗;播散性视网膜激光光凝