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Bevacizumab for the treatment of macular oedema in patients with diabetic retinopathy and retinal vascular occlusive disorders

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Aim To evaluate the efficacy of intravitreal bevacizumab injection in reduction of the central macular oedema (CME) in patients with diabetic retinopathy (DR) and branch or central retinal vein occlusion (BRVO, CRVO).

Material and methods In a prospective study were included 107 eyes of 96 patients (55 male and 41 female) with proliferative DR, type 2 diabetes and 31 eyes of 31 patients (13 male and 17 female) with RVO (16 with BRVO, 15 with CRVO) occurred maximum 1 month ago. All eyes were with CME. Three consecutive injections of dose 1.25 mg were performed at 4-weeks intervals. Best-corrected visual acuity (BCVA), central macular thickness, and complication rate were documented during the 16 weeks follow-up period.

Results In both groups of patients with DR and RVO, CME decreased progressively with every injection in comparison with baseline ($P < 0.001$). Vision improved or stabilized in patents with DR and BRVO. Despite the decreased CME, there was no significant functional improvement only in patients with CRVO. There were no significant side effects of intravitreal application of bevacizumab.

Conclusion Bevacizumab seems to stimulate the reduction of the CME in patients with DR and retinal vascular occlusive disorders within the first 8 to 12 weeks. These results are encouraging and merit further long-term investigation in larger scale studies.

Keywords: Central macular oedema (CME), Visual acuity (VA), Bevacizumab (Avastin), Diabetic retinopathy (DR), Branch retinal vein occlusion (BRVO), Central retinal vein occlusion (CRVO)

Introduction Although of differing aetiologies, both diabetic retinopathy (DR) and retinal vein occlusion (RVO) are associated with visual impairment due to retinal ischemia, macular oedema, non-resolving vitreous hemorrhage, and possibly retinal neovascularization (1, 2). The ischemia of RVO commonly results from narrowing of arteriovenous crossings and consequent venous compression (2), while in DR retinal vascular leukostasis, leading to capillary blockage and damage to the retinal vasculature, is believed to be a major contributing factor (1). GRID laser photocoagulation is an-evidence-based therapeutic option to reduce the macular oedema in patients with DR, branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) (1, 2, 3). However, over the past 15 years investigations into the underlying molecular and cellular mechanisms of ischemia-related vision loss have clarified the essential role of vascular endothelial growth factor (VEGF) in promoting both macular oedema and retinal neovascularization (4). VEGF increases retinal permeability, causes breakdown of the blood-retinal barrier and leads to macular oedema. Moreover, VEGF synthesis is unregulated by the hypoxia that accompanies retinal ischemia (5). As a result, ocular levels of VEGF are significantly increased in patients with RVO (6) and DR (4). According to these findings, anti-VEGF medications may have a critical role in prevention and/or treatment of macular oedema and iris neovascularization.VEGF-A is a prototype member of the VEGF family, which includes six principal isoforms. Bevacizumab (Avastin, Genentech, San Francisco, CA) is a humanized recombinant antibody that binds to all isoforms of VEGF. Intravitreal Bevacizumab (IVB) has been recently reported as a treatment modality for macular oedema in patients with diabetes and after RVO (6, 7).

In this study, we sought to evaluate the efficacy of IVB in reduction of the macular oedema in patients with DR or RVO.

Patients and methods In a prospective study were included 107 eyes of 96 patients (55 male and 41 female) with proliferative DR, type 2 diabetes and 31 eyes of 31 patients (13 male and 17 female) with

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RVO (16 with BRVO, 15 with CRVO) occurred maximum 1 month ago. All of them were with central macular oedema (CME). The mean age of patients with DR was 59.7 years (range, 41–74 years) and 68 years (range, 51–79 years) with RVO respectively. All patients gave their informed consent prior to their inclusion in the study with specific emphasis on the off-label character and possible side effects of Bevacizumab.

Inclusion criteria were: fundoscopically and angiographically diagnosed DR, BRVO or CRVO with CME of more than 250 μm (measured by OCT/SLO), best corrected decimal visual acuity ≤ 0.5, patient able to give informed consent.

Exclusion criteria were: pregnancy, cardiac or apoplexies incidence during the last 3 months, patient note able to give informed consent.

Intravitreal injection of Bevacizumab Three consecutive injections were performed at 4-weeks intervals. Injections were done under sterile conditions with topical anaesthesia. For both group of patients 1.25 mg (0.05 cc) Avastin was injected intravitreally with a 30-gauge needle through the pars plana in inferotemporal quadrant of the eye. All eyes underwent an ophthalmic examination, checking 1 and 7 days after each injection for intraocular inflammation and intraocular pressure rise. Complete ophthalmic examination, optical coherence tomography (OCT) and fluorescein angiography were performed before the first, second and third injections and 4 weeks after the last intervention. We also documented the development of best-corrected visual acuity (BCVA), central macular thickness, and complication rate (i.e. inflammation, endophthalmitis, increased intraocular pressure, progression in lens opacity, vitreous haemorrhage, retinal tears, retinal detachment, and thromboembolic events). Statistical analysis was performed with SPSS software (Statistical Package for Social Science version 13.0, SPSS). *T*-test and chi-square test were used.

Results

Diabetic retinopathy At the baseline examination, mean BCVA was 0.08 ± 0.84 (range 0.05–0.2). BCVA improved to 0.2 ± 0.75 (range 0.08–0.6) at the 4-week follow-up, 0.3 ± 0.55 (range 0.09–0.4) at week 8, 0.3 ± 0.85 (range 0.09–0.5) at week 12, and 0.3 ± 0.90 (range 0.1–0.7) at week 16 (Table 1).

Table 1 Visual and central macular thickness outcomes (mean ± SD) in patients with proliferative DR during follow-up examinations

Time	BCVA (decimal)	CMT (micron)
Baseline	0.08 ± 0.85	482 ± 158
Week 4	0.2 ± 0.75	374 ± 129
Week 8	0.3 ± 0.55	291 ± 114
Week 12	0.3 ± 0.85	263 ± 142
Week 16	0.3 ± 0.90	249 ± 106

BCVA=Best-corrected visual acuity, CMT=Central macular thickness.

These BCVA readings were all statistically significant improved compared to the baseline ($P < 0.001$). However, BCVA values at week 8 *vs.* week 12 and week 16 did not show statistically significant increase ($P > 0.05$). The dynamics of the central retinal thickness changes is presented on the same table (Table1). At the baseline examination, mean CMT was 482 ± 158 μm (range 514–396). In addition, the difference between the follow-up changes in CMT versus the baseline appeared 4 weeks after the first injection and persists until 16 weeks ($P < 0.001$). There was a progressive decreased of the CMT with every one injection. CMT at week 8 was statistically significant lower than those at week 4 ($P < 0.01$), and CMT at week 8 was significantly lower than those at week 12 ($P < 0.01$).

Retinal vein occlusion In patients with BRVO mean visual acuity increased by more than 3 lines compared to baseline at week 6 ($P < 0.001$) and was stable up to 16 weeks. These findings were comparable with the changes in the CME. In contrast, in patients with CRVO the visual acuity fluctuated between 0.03 and 0.04 and remained 0.02 at end of the study. However, CME decreased significantly at week 4 ($P < 0.001$) and was relatively stable up to the week 16 (Table 2).

Autonomic & Autacoid Pharmacology
2010, 30, 101–165

Table 2 Visual and central macular thickness outcomes (mean ± SD) in patients with BRVO and CRVO during follow-up examinations

Time	BRVO		CRVO	
	BCVA (decimal)	CMT (micron)	BCVA (decimal)	CMT (micron)
Baseline	0.09 ± 0.45	407 ± 126	0.02 ± 0.85	617 ± 214
Week 4	0.3 ± 0.65	301 ± 147	0.03 ± 0.65	318 ± 117
Week 8	0.4 ± 0.35	254 ± 102	0.04 ± 0.45	294 ± 128
Week 12	0.4 ± 0.75	242 ± 94	0.03 ± 0.25	278 ± 142
Week 16	0.4 ± 0.55	248 ± 106	0.02 ± 0.75	306 ± 114

BCVA=Best-corrected visual acuity, CMT=Central macular thickness, BRVO=Branch retinal vein occlusion, CRVO=Central retinal vein occlusion.

There were no significant side effects of IVB application in both groups of patients during the follow-up period. One eye with DR (0.93%) showed an intraocular pressure rise to 24 mmHg at 1 day after the injection. The elevated intraocular pressure was controlled with an anti-glaucoma drop (Cosopt).

Discussion With bevacizumab a new treatment option has been introduced for early intervention against the formation of CME (1, 6). Considering the severity of CME in patients with proliferative DR and RVO and in the attempt to maximize the potential effect of bevacizumab, we decided to perform three consecutive injections as a loading dose in our treatment strategy. In the group of patients with DR, the treatment effect was achieved at week 8 and remained relatively stable to the end of the study [Table 1]. Our results are comparable with those of Haritoglu *et al.* (8). In diabetes, VEFG is present in high concentrations and produced continuously. Is there a problem with attacking macular oedema with a relatively short-acting anti-VEGF agent? There was reported that primary IVB at doses of 1.25 to 2.5 mg seems to provide stability or improvement in visual acuity and CMT in eyes with diabetic macular oedema at 6 months (1).

Although the exact pathological sequence of RVO is unknown, visual acuity seems to be only depending on macular ischemia, but mainly on CME and photoreceptor damage in the early period of the disease. Both groups of patients with BRVO and CRVO with low as well as with high baseline CME benefited from bevacizumab injections. There was reported that the lowest mean level of CMT was achieved at week 12 (9). The evaluation of functional results showed differences in the positive impact of early treatment on visual acuity (9). In our study, most of the patients with BRVO improved the visual acuity significantly at week 8 after the second injection in comparison with baseline [Table 2]. The functional results remain stable to the end of the study. In the group of patients with CRVO mean CME decreased significantly, but despite the gut anatomical results, the visual acuity did not improve. It can be assume that the degrees of ischemia as well as other individual factors have an impact on treatment response.

In summary, an IVB injection seems to stimulate the reduction of the CME in patients with DR and retinal vascular occlusive disorders within the first 8 to 12 weeks. In general, vision improved or stabilized in patents with DR and BRVO. In contrast, no significant functional improvement was observed in patients with CRVO. These results are encouraging and merit further long-term investigation in larger scale studies.

References

1. GUARDIOLA, A.A., BUSQUETS, M.A. (2008). Diabetic macular oedema: treatment updates 2008. *Retina today*, 3, 38–41.
2. HEYREH, S.S. (2006). Venous occlusive disease: management 25 years ago. *Retina*, 26(6), 51–62.
3. The Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular oedema in central vein occlusion .*Ophthalmology*, 1995, 102, 1425–1433.
4. NGUYEN, Q.D., TATLIPINAR, S., SHAH, S.M. *et al.* (2006). Vascular endothelial growth factor is a critical stimulus for diabetic macular oedema. *Am. J. Ophthalmol.*, 142, 961–969.
5. AIELLO, L.P., NORTHRUP, J.M., KEY, B.A. *et al.* (1995) Hypoxic regulation of vascular endothelial growth factor in retinal cells. *Arch. Ophthalmol.*, 113, 1538–1544.
6. NOMA, H., MINAMOTO, A., FUNATSU, H. *et al.* (2006) Intravitreal levels of vascular endothelial growth factor and interleukin-6 are correlated with macular oedema in branch retinal vein occlusion. *Graefes Arch. Clin. Exp. Ophthalmol.*, 244, 309–315.

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Blackwell Publishing Ltd

Autonomic & Autacoid Pharmacology
2010, 30, 101–165

7. AHMADIEH, H., RAMEZANI, A., SHOEIBI, N. *et al.* (2008) Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular oedema: a placebo controlled, randomized clinical trial. *Graefes Arch. Clin. Exp. Ophthalmol.*, 246, 483–489.
8. HARITOGLU, C., KOOK, D., NEUBAUER, A., *et al.* (2006) Intravitreal bevaciuzumab (Avastin) therapy for persistent diffuse diabetic macular oedema. *Retina*, 26, 999–1005.
9. STAHL, A., AGOSTINI, H., HANSEN, L., FELTGEN, N. (2007) Bevacizumab in retinal vein occlusion-results of prospective case series. *Graefes Arch. Clin. Exp. Ophthalmol.*, 245, 1429–1436.

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