Bevacizumab for Macular Edema in Branch and Central Retinal Vein Occlusion

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Purpose: To assess the efficacy and safety of intravitreal bevacizumab in central and branch retinal vein occlusion.
Methods: Prospective study, 18 patients, 19 eyes in branch retinal vein occlusion, and 37 patients and 37 eyes in central retinal vein occlusion; preoperative and postoperative assessment: visual acuity, fundus biomicroscopy, optical coherence tomography (OCT).
Results: Visual acuity improves in 84% in central retinal vein occlusion (OVCR) and 73.33% in branch retinal vein occlusion (BRVO) at 1 month after the third injection.
Conclusions: Bevacizumab may play a role in the treatment of central and branch retinal vein occlusion.

Keywords: intravitreal bevacizumab, macular oedema, best corrected visual acuit, retinal vein occlusion.

Received: 7 May 2012

Introduction

Retinal vein occlusion (RVO) is the most common retinal vascular disease after diabetic retinopathy, with a prevalence of between 1% and 2% in persons older than 40 years [1,2].

Retinal circulation is ordinarily an end-artery system that does not communicate with the blood vessels of the choroid and ciliary body. Blockage of the retinal venous circulation thus leads to significant retinal damage with accompanying visual loss [3]. Early treatment may be required to improve vision, because longstanding macular edema results in irreversible photoreceptor damage.

Branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) have potential sight-threatening complications. The most common complication is the development of cystoid macular edema with a consecutive deterioration in vision. The major stimulus for the formation of macular edema and neovascularization in patients with RVO seems to be hypoxia-induced production of vascular endothelial growth factor (VEGF), an angiogenic factor that promotes angiogenesis and increases vascular permeability [4]. VEGF also stimulates endothelial cell hypertrophy, which reduces the capillary lumen and causes more ischemia, thus perpetuating the edema [5].

The agents that inhibit the effects of vascular endothelial growth factor, which is involved in the pathophysiology of macular edema, have been used in many cases in an off-label manner, to treat a variety of ocular diseases, including macular edema secondary to retinal vein occlusion, with satisfactory results [6].

Bevacizumab (Avastin; Genentech Inc, San Francisco, CA) is a monoclonal antibody that inhibits all isoforms of VEGF. Its use for RVO was first reported by Rosenfeld in 2005 [7].

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Several retrospective and prospective studies have shown the benefit of anti-VEGF treatment, with an improvement in visual acuity and a decrease of retinal thickness in patients with macular edema (ME) associated with RVO [8,9,10].

The purpose of this study is to evaluate the efficacy of intraocular injections with bevacizumab in patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO) and branch retinal vein occlusion (OVR).

Material and methods

We conducted a prospective, consecutive, non-comparative study. We reviewed data of patients who had macular edema secondary to retinal vein occlusion who were treated with bevacizumab (Avastin 2.5 mg/0.1 mL) and followed up with regular visits during at least 12 months. Patients were fully informed verbally about the experimental nature of the treatment and they signed an informed consent form.

Cases were recruited from the Ophthalmology Clinic of Tîrgu Mureş from January 2010 to November 2012. Inclusion criteria were: 1) macular edema secondary to RVO – macular swelling (quantitatively characterized by a macular thickness larger than 250 μm in any of the six radial scans), and 2) VA >0.01 (ETDRS chart). Exclusion criteria were: 1) any history of a recent thromboembolic event; 2) bleeding disorders.

A comprehensive ophtalmic evaluation was performed, including a medical history review, best corrected visual acuity testing (using ETDRS charts), slit-lamp biomicroscopy, dilated funduscopic examination using a 90-diopter lens and time domain ocular computed tomography – OCT (OCT III, Stratus OCT, Carl Zeiss, Germany), which consisted of an acquisition protocol "Radial lines" (6 linear, 6 mm scans oriented at intervals of 30° and centered on the foveal region). Macular maps were obtained using the "retinal thickness/volume" analysis protocol, and

Table I. Characteristics of patient groups

Parameter	Central retinal vein occlusion				Branch retinal vein occlusion			
	Female	Male	Total	p value	Female	Male	Total	p value
Affected eye								
Right eye	15	11	26 (56.5%)	0.74	7	7	14 (51.9%)	0.74
Left eye	7	13	20 (43.5%)		9	4	13 (48.1%)	
Total	22 (47.8%)	24 (52.2%)	46		16 (59.3%)	11 (40.7%)	27	
Age groups (years)								
<50	1	2	3 (6.5%)	0.93	1	2	3 (11.1%)	0.93
50-54	1	1	2 (4.3%)		0	1	1 (3.7%)	
55-64	7	6	13 (28.3%)		3	0	3 (11.1%)	
65-74	10	10	20 (43.5%)		8	6	14 (51.9%)	
75-85	3	5	8 (17.4%)		4	2	6 (22.2%)	
Total	22 (47.8%)	24 (52.2%)	46		16 (59.3%)	11 (40.7%)		

values for central foveal thickness (FT) and total macular volume (MV) were recorded. Follow-up examinations were scheduled at 1, 3, 6 and 12 months post-injection, or on demand, if a decrease in VA was noted by the patient. These follow-up examinations used exactly the same procedures as those used in the baseline visit. The incidence of adverse events were monitored throughout the study. The effects of treatment, both on VA and on anatomical changes in the macula shown by OCT, were evaluated. There was loss of follow-up in patients number.

Treatment procedure

Patients received an intravitreal dosage of bevacizumab of 2.5 mg (0.1 mL) at baseline and once every four weeks during the first three months (loading phase). All treatments were performed in the operating room using topical anaesthesia (Benoxi) under sterile conditions. Bevacizumab was injected (using a 30-G needle) through the inferotemporal pars plana, 3.5 mm (pseudophakic) or 4 mm (phakic) posterior to the limbus. A drop of ofloxacine was applied to the affected eye immediately after the procedure and again every 6 hours for 7 days.

Statistical analysis

Nonparametric statistics (Wilcoxon test and Kruskal Wallis test) for related samples were used to analyse BCVA and foveal thickness before and after bevacizumab injection. A p value <0.05 was considered to be statistically significant.

Results

Forty-six eyes of 46 patients with macular edema due to central retinal vein occlusion were treated with intravitreal injection of bevacizumab at baseline. The characteristics of the patients are presented in Table I.

Patients belonging to both CRVO and BRVO groups received a loading phase of three consecutive monthly injections of bevacizumab, then they were followed-up at 1, 3, 6 and 12 months after the last injection. Visual acuity testing and fundus biomicroscopy were performed at each visit. OCT performed at baseline and months 1, 3, 6 and 12 were compared. The number of patients, injections and reinjections belonging to each phase of the study are presented in Table II.

After the loading phase, bevacizumab retreatment was performed, in large part, based on OCT criteria: a loss of five letters of visual acuity in conjunction with intraretinal fluid on OCT or an increase of OCT central retinal thickness of at least 100 μm being indications for retreatment.

Visual acuity values at different control times are presented in Table III. In the CRVO group there was a statistically significant difference between baseline and control 1 (p<0.001), baseline and control 3 (p=0.03). If we follow the VA parameter evolution, we observe that there is an increase between VA1–VAC1, then a decrease in VAC3 and an increase again in VAC6. These oscillations are not statistically significant (p=0.15). At control 12 there were no statistically significant difference between the compared groups (p=0.49).

Table II. The moments of injections and reinjections

	A1	A2	A3	C1	C3	C6	C12	Total
Central retinal vein occlusion								
Eyes	46	41	35	31	25	21	16	
Injections	46	41	35					122
Reinjections				1	5	0	5	11
Branch retinal vein occlusion								
Eyes	28	28	23	18	15	11	8	
Injections	28	28	23					79
Reinjections				1	0	0	2	3

Table III. Visual acuity outcomes at different controls

	VA 1 (SD)	VA 2 (SD)	VA 3 (SD)	VA C1 (SD)	VA C3 (SD)	VA C6 (SD)	VA C12 (SD)
Central retinal vein occlusion							
Control 1 (n=31)	0.16 (0.21)	0.26 (0.24)	0.31 (0.27)	0.37 (0.29)			
Control 3 (n=25)	0.16 (0.19)	0.26 (0.25)	0.31 (0.28)	0.33 (0.29)	0.29 (0.25)		
Control 6 (n=21)	0.15 (0.19)	0.25 (0.26)	0.32 (0.29)	0.31 (0.28)	0.29 (0.25)	0.30 (0.32)	
Control 12 (n=16)	0.15 (0.20)	0.24 (0.27)	0.32 (0.32)	0.30 (0.30)	0.30 (0.27)	0.27 (0.32)	0.24 (0.29)
Branch retinal vein occlusion							
Control 1 (n=18)	0.23 (0.26)	0.34 (0.33)	0.38 (0.33)	0.40 (0.37)			
Control 3 (n=15)	0.17 (0.18)	0.27 (0.30)	0.29 (0.29)	0.31 (0.33)	0.29 (0.33)		
Control 6 (n=11)	0.15 (0.18)	0.26 (0.31)	0.29 (0.30)	0.30 (0.33)	0.28 (0.34)	0.32 (0.35)	
Control 12 (n=8)	0.18 (0.20)	0.32 (0.36)	0.32 (0.33)	0.35 (0.38)	0.36 (0.37)	0.46 (0.37)	0.43 (0.43)

Table IV. Change in visual acuity values at different control times

Parameter	Central retinal vein occlusion				Branch retinal vein occlusion			
	C1	C3	C6	C12	C1	C3	C6	C12
Number of patients	31	25	21	16	18	15	11	8
Gain ≥3 lines	19.3%	52%	47.6%	50%	44%	53.3%	45.4%	37.5%
Stable 1-3 lines	93.5%	88%	71.4%	68.7%	100%	86.6%	100%	66.9%
Lost≥ 3 lines	3.2%	4%	14.2%	25%	0%	6.6%	0%	12.5%

In the BRVO group, following the evolution of visual acuity and changes between baseline and control 1 we found no statistically significant difference between the four groups (p=0.47). There was an improvement in visual acuity from baseline to the end of the loading phase and this improvement continued to control 1. The mean VA presented an increase in the VA 1–VA C1 range, then this value started to decrease to control 3, with no statistically significant differences (p=0.75).

Visual acuity increased from baseline to control 1, then presented a decrease at control 3. At control 6 it presented a better value compared to the previous control. These oscillations were not statistically significant (p=0.68).

There was an improvement in visual acuity along the first 6 months (the number of followed eyes at control 12 was only 8), these values decreasing at the end of the study. There was no statistically significant difference between the compared groups (p=0.86).

Visual acuity measurements are presented as absolute values (mean ± standard deviation), as a mean change from baseline to month 12, and in terms of the number of patients with (i) a gain of ≥15 letters or 3 lines, (ii) a change of <15 letters or 3 lines (stable), or (iii) a loss of ≥15 letters or 3 lines (Table IV).

We describe a case of a central retinal vein occlusion with persistent macular edema. The OCT demonstrated intraretinal fluid with a central retinal thickness of 662 µm and VA was 0.1 (Figure 1). The patient was treated with 2.5 mg of intravitreal bevacizumab. At two months, visual acuity improved to 0.8 and OCT demonstrated resolved fluid with a central retinal thickness of 217 µm (Figure 2).

One other case presented a macular thickness of 605 µm shortly after detection of an acute branch retinal vein occlusion of the superotemporal arcade (Figure 3). Optical coherence tomography of the macula 1 month after the intravitreal injection of 2.5 mg bevacizumab showed resolution of macular oedema (Figure 4).

Discussions

Central retinal vein occlusion

The mean age of the 46 patients in our study (65.9 years) is similar to that previously found in other studies and shows

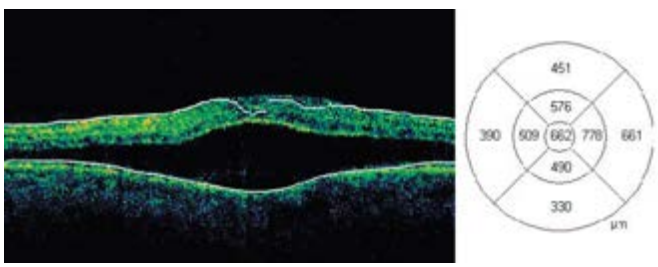

Fig. 1. Optical coherence tomography of the macula demonstrating extensive subretinal fluid prior to an intravitreal injection of 2.5 mg bevacizumab. The retinal thickness map shows a central elevation of the macula to 662 µm. Visual acuity was 0.1 (CRVO).

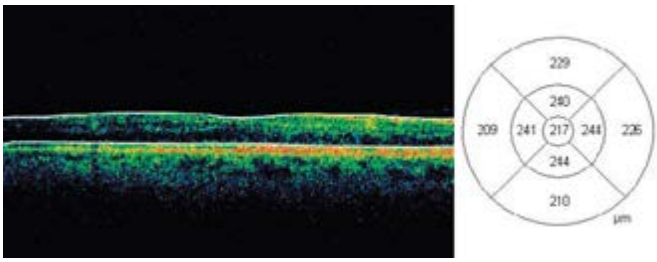

Fig. 2. Optical coherence tomography of the macula revealing resolution of subretinal fluid and restoration of macular anatomy at 2 months after an intravitreal injection of 2.5 mg bevacizumab. The retinal thickness map indicates a central thickness of 217 µm. Visual acuity was 0.8 (CRVO).

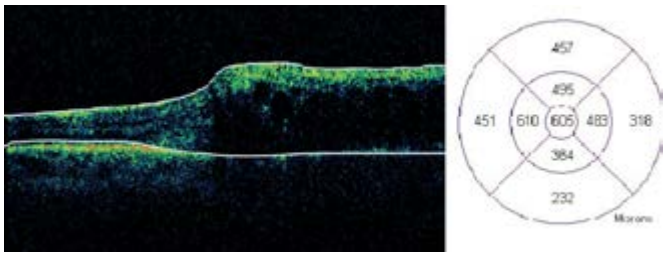

Fig. 3. Optical coherence tomography of the macula demonstrating a macular thickness of 605 µ in a patient shortly after detection of an acute branch retinal vein occlusion of the superotemporal arcade.

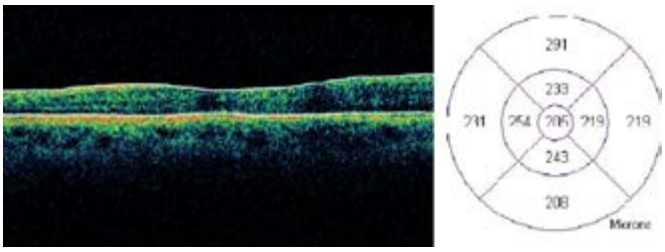

Fig. 4. Optical coherence tomography of the macula 1 month after an intravitreal injection of 2.5 mg bevacizumab with resolution of macular oedema

that CRVO is a disease of the elderly, but, although CRVO is less common in younger patients, it is by no means rare [11,12,13,14].

Of our patients 43.5% were aged 70 years or less and 28.3% aged 60 years or below. Follow-up data on visual recovery was available at the end of the study for 16 of our 46 patients and showed a generally good prognosis, as others have found in CRVO.

Florian Rensch and Jost B. Jonas in their study show that mean visual acuity improved significantly from 0.125 (0.97±0.40 logMAR) at baseline to 0.2 (0.70±0.42 logMAR) (p=0.007) at 1 month, 0.25 (0.69±0.46 logMAR) (p=0.006) at 3 months and 0.25 (0.69±0.52 logMAR) (p=0.015) at 6 months after the first injection. Mean central retinal thickness decreased significantly from 530±152 µm at baseline to 347±127 µm (p <0.001) at 1 month, 370±165 µm (p <0.001) at 3 months and 346±129 µm (p < 0.001) at 6 months (p <0.001) after the first injection. The increase in visual acuity correlated significantly (p <0.01) with the decrease in macular thickness [15].

In our study the mean VA at baseline was 0.16, which increased to 0.37 at C1, 0.29 at C3 and 0.24 at C12.

One month after the injection 6 patients (19.3%) showed an improvement of 3 or more lines. Three months after the injection 13 patients (52%) showed an improvement of 3 or more lines. Six months after the first injection 10 patients (47.6%) showed an improvement of 3 or more lines.

The mean change from baseline VA letter score at 12 months in central retinal vein occlusion patients was 11.5.

In our study the mean central retinal thickness decreased from 610 µm (37 eyes) at baseline to 296.6 µm (20 eyes) at the first control (p=0.001) and to 317.4 µm (5 eyes) at 3 months after the last injection (p=0.001)

The best visual acuity outcome was found at control one, after the loading phase. The highest rate of patients who gained more than 15 ETDRS letters, was found at control 3 (52%).

Branch retinal vein occlusion

The average age of the 27 patients was 66.2 years, with 11 men (40.7%) and 16 women (59.3%).

In this study we compared data of baseline values and after therapy with bevacizumab at 12 months. The results of this retrospective study showed that intravitreal bevacizumab treatment in patients with macular edema secondary to BRVO was associated with a significant improvement in visual acuity (from 0.18±0.20 to 0.43±0.43) at 12 months of follow-up and with a marked decrease in CRT (–217.6; p=0.003) at 1 month after the loading phase. We have no data about the CRT after the first control.

Mehmet et al. found similar results, the visual outcomes at 12 months improved from 0.23 (0.66±0.20 logMAR at baseline) to 0.63 (0.22±0.13 logMAR) [16].

Of 18 patients treated with bevacizumab for whom data were available at 1 month, 8 (44%) had improvement of 3 or more lines of VA and 18 (100%) had a stable visual outcome. At baseline, mean visual acuity was 46.54 letters (28 eyes) with an improvement of a mean of 17.9 letters at control three (15 eyes).

At the third control (15 eyes) the mean VA was 0.29 ± 0,33, 0.32 ± 0.30 at 6 months (11 eyes), and 0.43±0.40 (8 eyes) at 12 months. We mentioned that the followed patients decreased in number during our study. More than three lines of improvement were seen in 53.3% at control 3. Patients avoided the loss of 3 lines or less in 86.6% and it deteriorated in 6.6% at the 3-month follow-up.

Kort et al. found a mean VA of 0.1 at baseline, which improved significantly to 0.35 after 6 months. At 12 months the mean VA was 0.2. Mean CRT was 568 µm at baseline and decreased to 211 µm after 6 months and 223 µm at 12 months [17].

Mean VA at six month was 63.9 letters (improvement of 3 lines or more in 45.4%), and at the end of our study this dropped to 48 letters (gain of 15 letters or more in 37.5%). Like in central retinal vein occlusion, the best VA outcome was present at control one. The highest rate of the patients who gained more then 15 ETDRS letters, was found at control three (53.3%).

The results suggest a significant increase in visual acuity and, correspondingly, a significant decrease in macular oedema in patients who received an intravitreal injection of bevacizumab as treatment for CRVO and BRVO. The results confirm findings made on the intravitreal use of antiangiogenic drugs for the treatment of macular oedema secondary to RVO.

A point of special attention may be the dose of the intravitreal bevacizumab injection. Although there is no proven

therapy for this entity, intravitreal anti-vascular endothelial growth factor therapy has shown very promising results in the management of RVO.

Because this experimental intervention is widely accepted, one of the main concerns may now be related to dose safety and efficacy. While in most of the previous studies a dose of 1.25 mg of bevacizumab was used, a slightly higher dose (2.5 mg of intravitreal bevacizumab) was applied in the present investigation. It is questionable whether this relatively small difference in the doses may lead to major differences in the results of the studies when compared with each other.

There are limitations of the present investigation. The most important limitation is the lack of a control group. Because RVO shows a considerable rate of spontaneous improvement with regression of macular oedema, this spontaneous improvement may have mimicked a therapeutic effect of the intravitreal injection of bevacizumab in the present study.Therefore, the results of the survey suggest – but do not prove – that intravitreal bevacizumab may be helpful for the treatment RVO. Uncontrolled trials such as the present investigation and those mentioned previously on the same topic have an obvious methodological limitation, as discussed earlier. However, this aspect does not invalidate all the conclusions of these studies.

Another limitation of this study may be that the number of enrolled patients was relatively low. Despite this, the results showed a statistically significant improvement in visual acuity; the small number of patients may only serve to strengthen the results and conclusion of the study. Nevertheless, the number of patients included in the study is without doubt too low to allow a substantial statement about the safety of the treatment to be made. Another drawback is that the follow-up was not very long, so conclusions about the long-term effect of the treatment cannot be drawn. The results, as presented in the present study, have to be considered preliminary.

Conclusions

1. Intravitreal bevacizumab seems to be an effective primary treatment option for macular oedema due to retinal occlusions.
2. Intravitreal bevacizumab resulted in a significant decrease in macular edema and improvement in visual acuity.
3. The number of patients in this pilot study was limited and the follow-up is too short to make any specific treatment recommendations, but the favorable short-term results suggest further study is needed.
4. Its main drawback is that multiple injections are necessary to maintain visual and anatomic improvements.

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