ORIGINAL ARTICLE

EVALUATION OF THE EFFICACY AND SAFETY OF INTRAVITREAL BEVACIZUMAB FOR MACULAR EDEMA RELATED TO RETINAL VEIN OCCLUSION

CALIN PETRU TATARU[1,2], RALUCA IANCU[1,3]*, ANCA DOGAROIU[2], CAMELIA DIACONU[4], CATALINA CORBU[1,2]

[1]*UMF "Carol Davila", Ophthalmology Department, 8 Eroilor Sanitari, 050474, Bucharest, Romania*
[2]*Emergency Eye Hospital, 1 Al. Lahovary Square, Bucharest, Romania*
[3]*University Emergency Hospital Bucharest, 169 Splaiul Independentei, 050098, Bucharest, Romania*
[4]*Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, 8 Calea Floreasca, 014461, Bucharest, Romania*

**corresponding author: ralucavasile2002@yahoo.com*

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Abstract

This study was conducted to compare the efficacy and safety of bevacizumab used as an off-label intravitreal drug in patients with macular oedema (ME) secondary to branch and central retinal vein occlusion. This was a prospective, non-randomized cohort study which comprised 64 patients: 36 patients with macular oedema secondary to branch retinal vein occlusion (BRVO), and secondary to central retinal vein occlusion (CRVO) in 28 patients, who were treated primarily with intravitreal bevacizumab 1.25 mg/0.05 mL. During the minimum 6-months follow-up period, patients were examined after 1 month, 3 months and 6 months post--injection. The main outcome measures included: visual acuity, central macular thickness measured by Optical Coherence Tomography (OCT) and recurrence. At 6-months follow-up the best corrected visual acuity (BCVA) increased statistically significant when compared with preoperative values in both groups (p = 0.0024 for the BRVO group and p = 0.02 for the CRVO group). The most significant central macular thickness (CMT) improvement was achieved at 1 month follow up post-IVB. For the BRVO patients, baseline CMT was 362.7 ± 123 μm and at 1 month follow up CMT was 247.2 ± 114.1 μm. For the CRVO patients, baseline CMT was 424.0 ± 165.1 μm and at 1 month follow up CMT was 288.2 ± 58.7 μm. In the BRVO group, macular oedema recurred in 19.4% of the patients (7 patients) and for the CRVO group in 28.5% (8 patients). Intravitreal injection of bevacizumab for ME secondary to BRVO or CRVO was effective and generally safe in the first 6 months post-injection.

Rezumat

Acest studiu a fost realizat pentru a compara eficacitatea și siguranța administrării intravitreene a bevacizumab-ului la pacienții cu edem macular (EM) secundar obstrucției venei centrale a retinei sau a unui ram venos retinian. Studiul de față are design prospectiv, nerandomizat, de cohortă, ce cuprinde 64 de pacienți cu edem macular (în cazul a 36 de pacienți EM fiind secundar obstrucției unui ram venos retinian, iar în cazul a 28 de pacienți acesta a fost consecința obstrucției de venă centrală a retinei) tratați prin injecție intravitreană a 1,25 mg/0,05 mL bevacizumab. Ulterior pacienții au fost evaluați la 1 luna, 3 luni și respectiv 6 luni postoperator. Principalii parametri urmăriți au fost acuitatea vizuală (AV), grosimea centrală a maculei (GCM) evaluată prin tomografie de coerență optică (OCT) și recurența. La 6 luni postoperator acuitatea vizuală cu cea mai buna corecție optică s-a îmbunătățit semnificativ statistic comparativ cu valorile preoperatorii în cazul ambelor loturi de pacienți (în cazul pacienților cu obstrucție de ram venos retinian p = 0,0024, iar în cazul celor cu obstrucția venei centrale a retinei p = 0,02). GCM a înregistrat cea mai importantă reducere la o lună după injecția intravitreană cu bevacizumab. Pentru pacienții cu obstrucție de ram venos, valoarea medie preoperatorie a GCM a fost de 362,7 ± 123 μm, iar la o lună postoperator de 247,2 ± 114,1 μm. Pentru pacienții cu obstrucție de venă centrală a retinei, valoarea medie preoperatorie a GCM a fost de 424,0 ± 165,1 μm, iar la o lună postoperator de 288,2 ± 58,7 μm. În cazul pacienților cu obstrucție de ram venos retinian, edemul macular a reapărut în cazul a 19,4% dintre pacienți (7 pacienți), iar în cazul celor cu obstrucție de venă centrală a retinei, la 28,5% dintre pacienți (8 pacienți). Injecția intravitreană cu bevacizumab pentru edemul macular secundar obstrucțiilor venoase retiniene este eficace și în general sigură în primele 6 luni postoperator.

Keywords: bevacizumab, macular oedema, branch and central retinal vein occlusion

Introduction

Branch and central retinal vein occlusion (BRVO, CRVO) from all of retinal vasculature pathologies represent the most frequent cause of decreased visual acuity following diabetic retinopathy [20]. The decrease in visual acuity is due to the development of macular oedema (ME) which may occur at any stage of the disease. ME is a consequence of the dysfunction of the endothelial blood-retinal barrier and increased vascular permeability which lead to leakage. Vascular-

endothelial growth factor (VEGF) is known to play a major role in this increased vascular permeability [8].

Medications such as ranibizumab, pegaptanib, alfibercept and bevacizumab, act by inhibiting vascular endothelial growth factor (VEGF), thus preventing the angiogenesis. Intravitreal injection of VEGF inhibitors represent nowadays the main treatment for neovascular age-related macular degeneration and also represent a good option for ME related to BRVO and CRVO. Although only pegaptanib and ranibizumab are approved for the treatment of ophthalmological conditions, bevacizumab is also widely used in ophthalmology as an off-label drug since 2004 [16, 17].

Bevacizumab is approved by Food and Drug Administration (FDA) for the treatment of colo-rectal cancer [12]. Bevacizumab, better known under the common trade name Avastin®, is a full-length recombinant humanized monoclonal antibody that binds to and neutralizes the biologic activity of human VEGF.

In 1971, Judah Folkman reported in the "New England Journal of Medicine" that all malignant tumours are angiogenesis-dependent [7]; he was the first to use the term "anti-angiogenic therapy" and bevacizumab became the first therapy approved by the FDA to inhibit angiogenesis in tumours [10]. VEGF represents an angiogenic inducer *in vivo* and an endothelial cell-specific mitogen *in vitro*. VEGF is a dimeric glycoprotein of 36-46 kD which binds on the surface of endothelial cells and initiates endothelial proliferation and the formation of new blood vessels. This growth factor plays a key role in developmental angiogenesis, being one of the most potent positive regulators, and also demonstrated to act as a mediator of pathological angiogenesis [5]. Bevacizumab is a humanized monoclonal antibody, designed against the biologically active isoforms of VEGF [5]. It is derived from the murine VEGF monoclonal antibody, combining over 90% human protein sequence with about 7% murine protein sequence [19]. Bevacizumab has a molecular weight of about 149 kD, with the structure of recombinant IgG antibody.

Materials and Methods

This study was conducted in order to compare the efficacy and safety of bevacizumab used as an off-label intravitreal drug in patients with branch and central retinal vein occlusion, in the early period. The present study was designed as a prospective, non-randomized cohort study.

The study comprised of 64 patients - 36 patients who developed branch retinal vein occlusion and 28 patients diagnosed with central retinal vein occlusion - diagnosed and treated between January 2010 and September 2013. All the cases had systemic hypertension under medical treatment. No patient had history of thromboembolic events, known coagulation abnormalities or current use of anticoagulant medication other than aspirin, or other major systemic diseases. Diabetic patients with diabetic retinopathy were excluded. The patients did not have prior pars plana vitrectomy, intraocular injection, macular lesions, intraocular surgery, except uneventful phacoemulsification, laser photocoagulation or ocular trauma. Presence of other ocular conditions causing macular oedema (diabetic macular oedema, pseudophakic cystoid macular oedema and uveitis) represented exclusion criteria.

Macular oedema was defined as macular leakage on fundus fluorescein angiography and central foveal thickness (CFT) more than 250 μm detected by optical coherence tomography (*Topcon* 3D *OCT*-2000, Topcon Corporation Tokyo, Japan) with macular pathologies including cystoid changes and diffuse thickening. Patients with vitreomacular traction or epiretinal membrane were excluded.

Best-corrected visual acuity (BCVA) in Snellen chart and ophthalmic examination procedures including optical coherence tomography (*Topcon* 3D *OCT*-2000, Topcon Corporation Tokyo, Japan) were performed prior to injection and after 1 month, 3 months and 6 months post intravitreal bevacizumab administration (1.25 mg/0.05 mL – Avastin®).

We have complied with the Declaration of Helsinki to perform this study. After detailed explanation of risks, benefits, and off-label use of these medications, all the participants signed the informed consent before the intravitreal injections. The procedures were performed at Emergency Eye Hospital, Bucharest, by two surgeons. The study was approved by the Hospital's Ethics Committee.

Following topical anaesthesia and disinfection of eyelid and conjunctiva, bevacizumab was injected into the vitreous cavity using a 30-gauge needle inserted through the superotemporal pars plana, 4 mm posterior to the limbus. After the procedure, tetracycline ointment was placed into the conjunctival sac. The eye was patched for one day. The patient was advised to administer one drop of moxifloxacin into the injected eye four times daily for one week. The complications after injection were recorded.

The main outcome measures included: *function*, consisting in visual acuity (VA) and *structure*, represented by central macular thickness measured by OCT and recurrence.

Results and Discussion

Baseline data

The present study included 64 patients that developed macular edema secondary to BRVO or CRVO. All patients received one IVB injection and were followed up for at least 6 months. The mean

follow up for BRVO group was 11.3 ± 7.4 months and for CRVO group was 13.3 ± 4.8 months. To compare the recurrence of macular oedema of one IVB, all patients were included for Kaplan – Meier statistical analysis. There were no statistically significant differences between the two groups regarding age, sex distribution and comorbidities. A p value less than 0.05 was considered statistically significant.

Visual acuity

The visual acuity (VA) was determined pre-operatively at 1, 3 and 6 months postoperatively. At 6 months follow up, visual acuity increased statistically significant compared with preoperative values in both groups. For the BRVO group, the mean BCVA increased from 0.18 (Snellen chart) preoperative to 0.37 at 6 months, while for the CRVO group mean BCVA increased from 0.1 preoperative to 0.24 (Figure 1). The visual acuity at 6 months was statistically significant improved compared with preoperative status in both groups (p = 0.0034 for the BRVO group and p = 0.02 for the CRVO group).

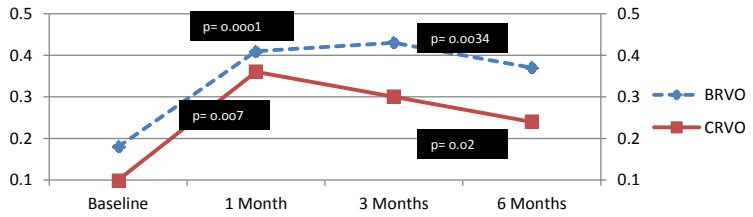

Figure 1.
Visual acuity changes (Snellen chart) for both groups after IVB

Central macular thickness

Significant central macular thickness (CMT) improvement was achieved at 1 month follow up post-IVB injection. For the BRVO group, baseline CMT was 362.7 ± 123 µm and at 1 month follow up CMT was 247.2 ± 114.1 µm. For the CRVO group, baseline CMT was 424.0 ± 165.1 µm and at 1 month follow up CMT was 288.2 ± 58.7 µm (Figure 2).

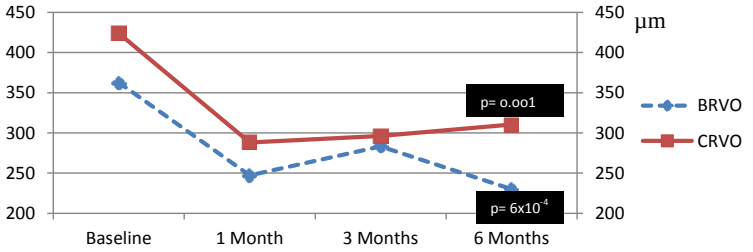

Figure 1.
Central macular thickness changes after IVB for both groups

Macular oedema recurrence

In the BRVO group, macular oedema recurred in 19.4% of patients (7 patients) and for the CRVO group in 28.5% (8 patients). The mean recurrence time was 5.8 ± 2.4 months for the BRVO group and 4.4 ± 3.6 months for the CRVO group. Kaplan-Meyer survival analysis of macular oedema recurrence showed higher recurrence incidence in the CRVO group (Figure 3).

In Table I are listed the reported ocular complications; the most common was the transient elevated intraocular pressure.

The most frequent non-ocular adverse effect was represented by arterial hypertension. In Table II are listed the rates of all systemic adverse effects.

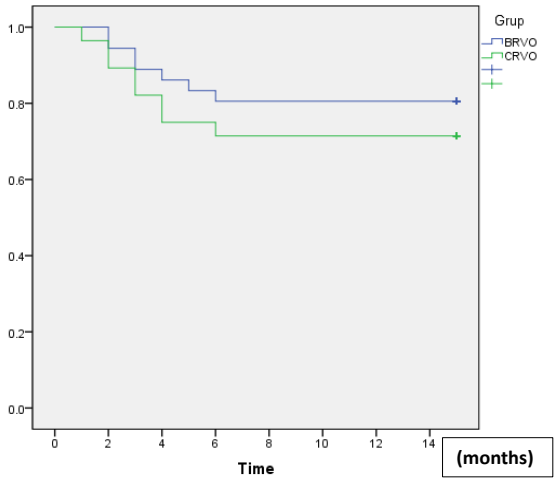

Figure 3.
Kaplan-Meyer analysis for macular edema recurrence after IVB (the BRVO group (blue line) 80.06% - no

recurrence, the CRVO group (green line) 71.50% - no recurrence)

Table I

Ocular complications that occurred after IVB injection

Reported ocular complications after IVB injection	BRVO (%)	CRVO (%)
Transient elevated intraocular pressure	11.11	7.14
Subconjunctival haemorrhage	5.55	7.14
Vitreous haemorrhage	0	3.57

Table II

Non-ocular complications that occurred after IVB injection

Reported adverse events after IVB injection	BRVO (%)	CRVO (%)
Systemic hypertension	13.89	10.71
Urinary tract infection	0	3.57
Cerebrovascular accident	0	3.57

Despite the fact that bevacizumab is not approved for treating ocular pathology, it is often used as an off-label treatment considering its low price compared to other licensed anti-VEGF agents (Ranibizumab).

This study was designed to analyse the efficacy and safety of bevacizumab, injected intravitreal for macular oedema secondary to BRVO and CRVO. Regarding the efficacy, IVB injection provided visual and anatomic improvements (statistically significant at 1, 3 and 6 months). Our results confirmed the existing data in the literature about the efficacy of bevacizumab as an off-label drug for macula oedema following retinal vascular disease [2, 9, 18].

The mean improvement of BCVA was 2.4 lines at 1 month, which was maintained throughout the first 6 months after IVB. The BRVO patients did show a better VA improvement compared to CRVO patients.

Mean central macular thickness was reduced in the majority of cases in both groups after IVB. Re-injection was considered when patients manifested an increase in central macular thickness (greater than 125 μm) or when VA decreased with more than one line on Snellen eye chart. We considered these events recurrences (7 patients in BRVO group and 8 patients in CRVO group).

Although in the majority of literature studies, IVB injection for ME secondary to BRVO and CRVO determined a significant improvement in VA [3, 4, 11, 14], the optimal treatment protocol remains unknown. A report on anti-VEGF pharmacokinetics administrated intravitrealy in rabbits suggested that bevacizumab has a longer intravitreal half-life that ranibizumab due to its glycosylated structure [1, 15]. This may suggest than bevacizumab may not require monthly injections to achieve an optimal therapeutic response [4, 11, 13].

Bevacizumab following intravitreal injection gains access into the systemic circulation. This anti-cancer drug found its way in ophthalmology and clinical practice all around the world, because the costs of the therapy with bevacizumab are much lower than with other similar VEGF inhibitors. Systemic hypertension, infections, thromboembolic diseases or even death can occur after systemic VEGF blockade [12, 21, 22]. In our study, the most frequent systemic adverse event was represented by transient mild rise in systemic blood pressure, seen in 8 patients (5 patients in BRVO group and 3 patients in CRVO group). The event occurred in the first week after IVB, but we can assign these changes to normal physiological diurnal variations or linked to surgery-related stress. Patients did not undergo cardiovascular examination; therefore, in this study, the adverse events are probably underestimated.

Conclusions

IVB injection for ME secondary to BRVO or CRVO was effective and generally safe in the first 6 months post-injection. To adequately monitor the chronic inhibition of VEGF given by bevacizumab, continuous monitoring of the adverse side effects in patients with IVB is essential to ensure the best care.

Acknowledgements

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