

Adverse Events Associated with Intraocular Injection of Anti-VEGF (bevacizumab) in Retinal Vein Occlusion: A Case Report

Elena Pacella¹, Paolo Turchetti², Marco Artico¹, Carmen Domenica Piraino¹, Antonella Mollicone¹,
Andrea Bottone¹, Francesca Romana Parisiella³, Fernanda Pacella^{1,*}

¹Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome, Italy

²National Institute for Health, Migration and Poverty (INMP/NIHMP), Rome, Italy

³Towson University, Baltimore, USA

*Corresponding author: fernanda.pacella@gmail.com

Received March 19, 2015; Revised March 30, 2015; Accepted April 02, 2015

Abstract Introduction: Antiangiogenic agents are often administered for treatment of Branch Retinal Vein Occlusion (BRVO). Among them, Bevacizumab has noticeable antiangiogenic and antiedemogenic properties and possesses great capacity to penetrate the retinal tissue, particularly in pathological circumstances characterized by altered external or internal blood-retinal barrier. Bevacizumab has an optimal bio-efficacy based on inhibition of the activity of Vascular Endothelial Growth Factor (VEGF). Nonetheless, despite its efficacy, here we describe the adverse effects associated with intraocular injection of bevacizumab in a patient affected by retinal vein occlusion.

Case presentation: We present a case report of an 11-year old Caucasian male subject affected by BRVO in his left eye. The patient underwent an intra-vitreous (i.v.) injection of bevacizumab 100 (1.25 mg/0.05ml). After that, the patient was monitored over time through a series of analyses including Ocular Coherence Tomography, Fluorangiography, Bulbar Ultrasound, Angio MRI BCVA scores and Intra Ocular Pressure. **Results:** Immediately after the i.v. injection, the patient experienced a strong and relentless pain radiating from the left ocular orbit, caused by a serious and unexpected malignant glaucoma and phthisis bulbi. Furthermore, the patient did not show any sign of improvement in visual function in the follow-up and at last required an ophthalmic prosthesis as a result of a sub-atrophic and hypotonic eyeball. **Conclusion:** This case report suggests that i.v. injections of anti-VEGFs should be considered with caution when treating central and branch vein occlusion, and are not free of complications in certain clinical cases.

Keywords: retinal vein and vascular occlusion, macular edema, intravitreal anti-VEGF, malignant glaucoma

Cite This Article: Elena Pacella, Paolo Turchetti, Marco Artico, Carmen Domenica Piraino, Antonella Mollicone, Andrea Bottone, Francesca Romana Parisiella, and Fernanda Pacella, "Adverse Events Associated with Intraocular Injection of Anti-VEGF (bevacizumab) in Retinal Vein Occlusion: A Case Report." *Neuro-Ophthalmology & Visual Neuroscience*, vol. 1, no. 1 (2015): 22-26. doi: 10.12691/novn-1-1-5.

1. Introduction

Branch Retinal Vein Occlusion (BRVO) is the most frequent vascular pathology after diabetic retinopathy, with an incidence of about 2.14/1000 per year in the population over 40 [1,2]. This condition is characterized by retinal ischemia, neo-vascularization, intra-retinal sector haemorrhages and macular edema (ME). This pathology causes an immediate loss of visual acuity due to a series of physiopathological events, such as reduced capillary perfusion (with consequent retinal hypoxia) and an increased hydrostatic pressure resulting in haemorrhage and exudation of fluid [3]. So far, the preferred treatment modality is the laser photo-coagulation, although new therapies based on intra-vitreous (i.v.) administration of anti-vascular endothelial growth factor (VEGF) and cortisone have been more recently introduced [4,5,6].

VEGF is the biggest angiogenic stimulus responsible for the development of anomalous blood vessels in retinal vascular pathologies [7]. It has been demonstrated that intra-vitreous VEGF levels are significantly increased after central retinal vein occlusion, and, in case of ischemia, this increase may lead to loss of tight junctions, vascular leakage and ultimately edema [8]. Accordingly, nowadays it is recognized that the use of anti-VEGFs may improve the state of retinal micro-circulation [9].

Bevacizumab, a full-length humanized monoclonal antibody, is a VEGF inhibitor initially used in the treatment of metastatic colon-rectal cancer [10], and successively adopted to treat neovascular retinal diseases [11]. The mechanism of action of bevacizumab is different from that of other anti-angiogenic compounds. While pegaptanib and ranibizumab penetrate the retina and reach the choroid, bevacizumab penetrates directly into the choroid, thus closing anomalous blood vessels [12]. This medication (given i.v.) is currently in use for the treatment

of different pathologies, such as Choroidal Neo Vascularization (CNV) caused by Age related Macular degeneration (AMD) [13,14], central retinal vein occlusion (CVO) [15], Diabetic Macular Edema (DME) and proliferative diabetic retinopathy (PDR) [2]. Here we present a case of ocular complications in a patient affected by retinal vein occlusion and treated with intraocular injection of bevacizumab.

2. Case Presentation

In November 2013, a 11-years old patient with a 2-months history of blurred and distorted vision in left eye (LE) was admitted to our observation unit. Amsler grid test showed metamorphopsia in the LE and normal findings in the right eye (RE). The examination of the anterior segment was normal, and intra-ocular pressure (IOP) was 16mmHg in both eyes. Best corrected visual acuity (BCVA) was 20/50 in the LE and 20/20 in the RE.

Biomicroscopic examination of the ocular fundus revealed a central retinal vein occlusion with macular edema, confirmed by optical coherence tomography (OCT), an alteration of the chorio-capillary barrier and epithelial pigment, and increased foveal thickness (FT) 480 micron (Figure 1).

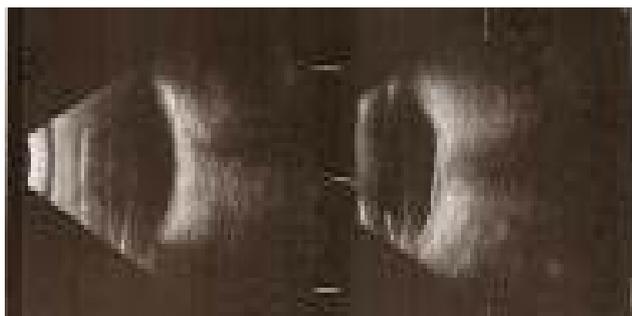


Figure 1. Bulbar ultrasonography: Vitreous dis-homogeneity left eye (LE) > right eye (RE).

LE: liquid type alterations of the retinal profile in the posterior pole with involvement of the macula and optic disc. Edema of the optic nerve sheath.

A bulbar ultrasonography revealed a vitreous dyshomogeneity in the LE, with liquid type alterations of the retinal profile in the posterior pole, with involvement of the macula and optic disc. An edema of the optic nerve sheath was present, with no evidence for expansive pathologies at the orbital site.

Fluorescein angiography (FA) showed a picture of BRVO of ischemic-hemorrhagic type, with hyper-fluorescence of the optic disc in the LE (Figure 2, Figure 3).



Figure 2. Ultrasonography orbital: Non evident expansive pathologies at the orbital site. Para-nasal sinuses well evident. RE: retina always on plane and acoustic wave of the optic nerve within standard limits

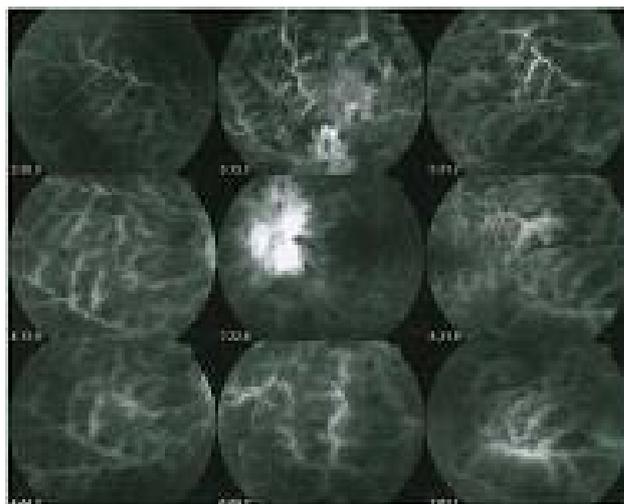


Figure 3. Fluorescein angiography (FA): BRVO of the ischemic-hemorrhagic type. Hyper-fluorescence of the optic disc in the left eye (LE) and no alterations of the hemo-retinal barrier (HRB) in right eye (RE)

The RE did not present alterations of the blood-retinal barrier (BRB), with retina always on plane and acoustic wave of the optic nerve within standards (Figure 2, Figure 3).

Routine Blood tests showed the following altered values: alkaline phosphatase (283 IU/L, range 42-121 IU/L); anisocytosis (RDW 18.5%, range 10-16%); hyperchromia and microcytosis (MCV 65 fl, range 80-100; MCH 19.4 pg, range 26-34 pg), and neutropenia (NEU% 43.2, range 50-80%). Immunological tests, anti-viral antibodies, anti-Toxoplasma, and VDRL were all negative.

2.1. Neurological Examination

Brain and Angio MRI showed a normal appearance of internal carotid arteries and their principal intracranial afferents. There were no evident alterations in the vertebro-basilar region and a representation of the principal intra-cranial venous branches with normal limits. Fearing a possible thrombosis or onset of a carotid dural cavernous fistula, an arteriography was proposed to the patient's parents, but they did not give consent to this diagnostic procedure.

2.2. Initial Treatment

With informed consent, the patient was initially treated with a symptomatic general therapy consisting of selegiline (2850UI/0.3ml 2 fl. subcutaneously), Prednisolone (25 mg/day, os), acetazolamide (250 mg/day, os) specifically indicated in the treatment of ocular hypertension, gastric protectors (150 mg/day, os) and a food supplement (one tablet/day).

2.3. Bevacizumab Intravitreal Injection and Follow-up Complications

Not noticing any improvement in child's condition, the parents decided to take him to another hospital where he was subjected to intravitreal injection (i.v.) of bevacizumab 100 (1.25mg/0.05ml) to his LE.

Few hours after the injection, the patient complained intense pain in the LE and was brought again to our attention. His IOP in his LE was now 64mmHg. The patient was immediately treated with endovenous mannitol

(250mg×2) (drop infusion), acetazolamide (250 mg os; three tablet/ day) and topical atropine. To reduce pain and congestion, steroids, timolol drops, and carbonic anhydrase inhibitors were also administered.

After a week, the pain was still relentless and unbearable and his IOP was 52mmHg. Thus, to manage the pain an elastomeric pump was implanted and used to administer ketorolac, initially at a dose of 90mg and successively 48 mg (2 mg/h × 24h).

Moreover, 20 applications of cyclo photocoagulation with YAG- laser free running mode (5.5 J) in the inferior section of the eye-ball (2.5 mm from the limbus) were given. During this time, haloperidol (1 mg) and orphenadrine hydrochloride (50 mg) were prescribed to the patient because of his altered psycho-physical condition.

A new bulbar ultrasonography was repeated in the LE. A marked dyshomogeneity vitreous inflammation was found, together with signs of retinal detachment (RD) of papillary origin and involving the macula of all the temporal sector of the eye (Figure 4). FAG also showed evidence of peri-papillary hemorrhage in RE (Figure 5, Figure 6).



Figure 4. Bulbar ultrasonography at 20 days from the acute events in the LE: Marked dis-homogeneity vitreous inflammation. Altered retinal profile for retinal detachment (RD) of papillary origin and involving the macula of all temporal sectors of the eye

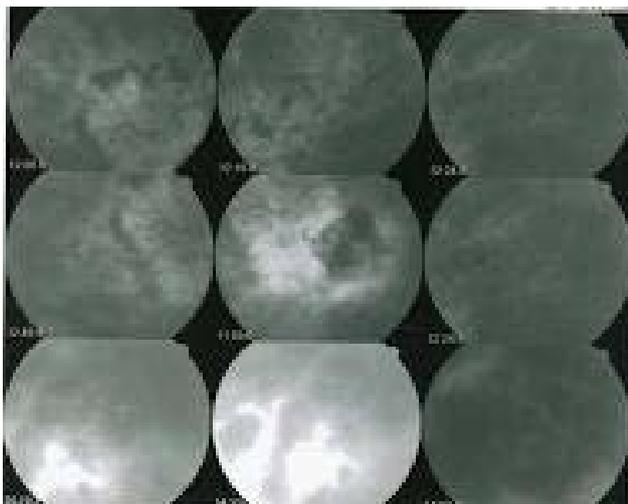


Figure 5. FAG showed evidence of peri-papillary hemorrhage in right eye (RE)

After 1 and 2 months from the acute event, LE visual acuity (AV) had markedly worsened to hand motion (HM). Rubeosis iridis was present at objective examination and IOP was 44 mmHg. A diffuse edema retinal was present and barely investigable because of an endovitreous hemorrhage. This edema was principally located in the posterior pole of the fundus, which was lifted at ophthalmoscopic examination. Bulbar Ultrasound (Figure 7)

produced pathological echoes in the vitreal chamber, attributable to endovitreous hemorrhage with a posterior detachment of the vitreous membranes. The retinal alteration in the posterior pole was associated to organized exudation and retinal detachment.

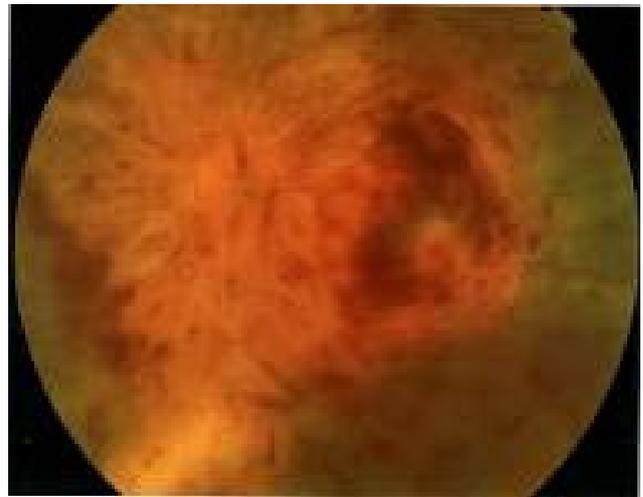


Figure 6. FAG showed evidence of peri-papillary hemorrhage in the right eye (RE)



Figure 7. Bulbar ultrasonography: Pathological echoes in the vitreal chamber attributable to endovitreous hemorrhage with a posterior detachment of the vitreous membranes, particularly in the superior section

Four months after the acute event, LE IOP progressively diminished to 23 mmHg with a consequent reduction of pain. Nonetheless, the patient showed athalamia and massive neo-vascularization, possibly evolving in a bulbar phthisis.

After one year, the patient required an ocular prosthesis, as a result of a subatrophy and hypotonic eyeball without signs of flogosis.

3. Discussion

Macular edema (ME) is the most frequent cause of loss of vision [1,2,3] and is generally treated with either focal photocoagulation [4,5] or, more recently, with i.v. triamcinolone [6]. However, laser photocoagulation causes an irreversible destruction of para-central retinal tissue and thus new treatment modalities have been developed.

Anti-angiogenic drugs, like corticosteroids, ranibizumab, pegaptanib and bevacizumab, represent new treatment options for ME without causing tissue damage [9,16,17]. In particular, antiangiogenic drugs may be useful for reducing both edema and neo-vascularization in occlusive pathologies [9,12,15]. Among them, bevacizumab,

administered i.v., has become the reference treatment option for the cure of ocular occlusive pathologies [16,18]. When compared to the traditional laser therapy, bevacizumab has been shown to induce comparable and significant improvements in patients affected by ME secondary to branch retinal vein occlusion (BRVO), both with chronic [19] or acute i.v. administration [20,21].

In case of BVRO, the optimal treatment strategy is still matter of debate. Natarajan (22) states that, in the majority of cases of Central Vein Occlusion (CVO), the disease may undergo to spontaneous regression after 3 months. However, in the CVO case reported here, no improvement in BCVA and ME was observed. Therefore, after 20 days of retinal vein occlusion (RVO), the patient underwent a fluorangiography (FAG) in order to establish the more appropriated therapeutic approach [16]. Photocoagulation or laser therapy could not be adopted because ME was such extensive to limit their efficacy [18,24]. Thus, as the patient did not show any improvement in his visual function during time, his parents decided to subject him to i.v. injections of bevacizumab in another health institute. The bevacizumab i.v. injection did not improve his retinal condition, and on the contrary provoked a greater dilation and an entanglement of the retinal veins, also evidenced by the FAG [12].

The reason for this failure is not clear. Bevacizumab is a drug inhibiting the development of neovascularization by blocking the molecular pathways of VEGFs and on their pro-angiogenic input [11,12]. Although this pharmacological action has been shown to be beneficial in case of ocular occlusive pathologies, the physiopathological mechanisms underlying RVO [23,24] and the role of VEGFs in ME [25] remain to be determined. Experimental studies suggest that VEGFs may also play a protective role in the hemo-dynamics of the retina and even a direct retinal neuroprotective role, particularly in hypoxic conditions [18,25]. In a recent review by Manousaridis and Talks [26], it is evidenced that in case of venous occlusion VEGFs promote the restoration of venous flow through the formation of blood vessels and blood perfusion in retinal unperfused areas, thus preventing ischemic lesions in the retina [9,25]. In addition, studies performed in primates have shown that anti-VEGF treatment reduces chorio-capillary fenestrations of retinal endothelial cells, increasing the ischemic damage in the internal retina [3].

These studies suggest that the blockade of VEGF action in cases of significant ischaemia at baseline may be detrimental to the retinal circulation. Supporting this notion, it has been demonstrated that repeated injections of bevacizumab may cause harmful effects on neuronal viability of retinal ganglion cells in rats [27]. In humans, retinal detachment (retinal pigment epithelium RPE) has been reported in two patients after repeated bevacizumab injections [24] while in a study of 707 patients both systemic and local complications were reported, although in minimal percentages [17]. Systemic complications included cerebral infarct, elevated systolic pressure, skin rashes and irregular periods while the most common local complications were corneal abrasions, lesions of the crystalline, inflammation, RPE detachment, and loss of vision [22]. These and other data have led to the suggestion that maintaining a normal balance between antiangiogenic and proangiogenic VEGFs (VEGF

165/VEGF165b) would be a more suitable approach, instead of only targeting proangiogenic VEGFs [7,18,25,28]. However, it should be noted that in the present case report bevacizumab injection was performed in another health institute and consequently we lack necessary information on the accuracy of the procedure adopted or other possible complications arisen during that period.

4. Conclusions

In conclusion, in the case report just presented, the decision to use i.v. bevacizumab injections did not prove to be the best choice as the results were dramatic. Ultimately, the patient was forced to adopt an ocular prosthesis because of the resultant phthisis. Although anti-VEGF agents are used in the management of ME with retinal vein occlusion [25,26,29], we believe that these therapies should be considered with caution because of the insufficient knowledge of the physiopathological mechanisms by which they act in retinal occlusive pathologies. In addition, further studies are necessary to establish the optimal dose range in young patients, as compared to adults.

List of abbreviations

Best corrected visual acuity (BCVA), Branch Retinal Vein Occlusion (BRVO), blood-retinal barrier (BRB), Choroidal NeoVascularization (CNV), central retinal vein occlusion to (CVO), Diabetic Macular Edema (DME), Fluorescein angiography (FA), hemo-retinal barrier (HRB), intraocular pressure (IOP), intra-vitreous (i.v.), Left eye (LE), Right eye (RE), macular edema (ME), optical coherence tomography (OCT), proliferative diabetic retinopathy (PDR), Retinal detachment (RD), Vascular Endothelial Growth Factor (VEGF), visual acuity (AV).

Consent

"Written informed consent was obtained from the parents of the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal."

Acknowledgements

We thank Professor Deodata Pacella.

Author Contributions

Conceived and designed the experiments: EP, FP, CDP, Analyzed the data: EP, FP, PT, CDP, MA. Wrote the first draft of the manuscript: FP, EP, CDP. Contributed to the writing of the manuscript: FP, PT, CDP, MA, FRP. Agree with manuscript results and conclusions: EP, FP, PT, CDP, FRP. Jointly developed the structure and arguments for the paper: EP, FP, PT, AM, CDP, FRP. AB. Made critical

revisions and approved final version: EP, FP, PT, MA, CDP, AB. FRP.

Statement of Competing Interests

The authors declare that they have no competing interests.

References

- [1] Klein, R., Klein, B., Moss, S.E., et al, "The epidemiology of retinal vein occlusion: The Beaver Dam Eye Study," *Trans Am Ophthalmol Soc*, 98, 133-41. 2001.
- [2] Eye Disease Case-Control Study Group, "Risk factors for branch retinal vein occlusion," *Am J Ophthalmol*, 116, 286-96.1993.
- [3] Ferrara, N., "Vascular endothelial growth factor: basic science in clinical progress," *Endocrinol Rev*, 25, 581-611.2004.
- [4] Branch Vein Occlusion Study Group, "Argon laser photocoagulation for macular edema in branch vein occlusion," *Am J Ophthalmol*, 98, 271-82.1984.
- [5] Branch Vein Occlusion Study Group, "Argon laser scatter photocoagulation for prevention of neovascularization and vitreous hemorrhage in branch vein occlusion: A randomized clinical trial," *Arch Ophthalmol*, 104, 34-41.1986.
- [6] Cekic, O., Chang, S., Tseng, J.J., et al, "Intravitreal triamcinolone injection for treatment of macular edema secondary to branch retinal vein occlusion," *Retina*, 25, 851-5.2005.
- [7] Finkelstein D, Ischemic macular edema: Recognition and favorable natural history in branch vein occlusion," *Arch Ophthalmol*, 110, 1427-34.1992.
- [8] Noma H., Funatsu H., Yamasaki M., et al, "Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6," *Am J Ophthalmol*, 140, 256-61. 2005.
- [9] Pacella, E., Pacella, F., La Torre, G., et al, "Testing the effectiveness of intravitreal Ranibizumab during 12 months of follow-up in venous occlusion treatment," *Clin Ter*, 163(6), e413-22. Nov. 2012.
- [10] Tashiro, A., Tatsumi, S., Takeda, R., et al, "High expression of organic anion transporter 2 and organic cation transporter 2 is an independent predictor of good outcomes in patients with metastatic colorectal cancer treated with FOLFOX-based chemotherapy," *Am J Cancer Res*, 4(5), 528-36. 2014.
- [11] Michels, S., Rosenfeld, P.J., Puliafito, C.A., et al, "Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study," *Ophthalmology*, 112(6), 1035-47. 2005.
- [12] Avery, R.L., "Regression of retinal and iris neovascularisation after intravitreal injection of bevacizumab (avastin) treatment," *Retina*, 26, 352-4.2006.
- [13] Nguyen, Q.D., Shah, S., Tatlipinar S., et al, "Bevacizumab suppresses choroidal neovascularisation caused by pathological myopia," *Br J Ophthalmol*, 89(10), 1368-70. 2005.
- [14] La Torre, G., Pacella, E., Saulle, R., et al, "The synergistic effect of exposure to alcohol, tobacco smoke and other risk factors for age-related macular degeneration," *Eur J Epidemiol*, 28(5), 445-6. May 2013.
- [15] Iturralde, D., Spaide, R.F., Meyerle, C.B., et al, "Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: a short-term study," *Retina*, 26(3), 279-84.2006.
- [16] Hayreh, S.S., Zimmernam, B., McCarthy, M.J., et al, "Systemic diseases associated with various types of retinal vein occlusion," *Am J Ophthalmol*, 131, 61-77.2001.
- [17] Shima, C., Sakaguchi, H., Gomi, F., et al, "Complications in patients after intravitreal injection of bevacizumab," *Acta Ophthalmol*, 86(4), 372-6.2008.
- [18] Hayreh, S.S., and Zimmerman, M.B., "Branch retinal vein occlusion: natural history of visual outcome," *JAMA Ophthalmol*, 132(1), 13-22.2014.
- [19] Jaisse, G.B., Leitritz, M., Gelisken, F., et al, "One-year results after intravitreal bevacizumab therapy for macular edema secondary to branch retinal vein occlusion," *Graefes Arch Clin Exp Ophthalmol*, 247(1), 27-33.2009.
- [20] Batioğlu, F., Astam, N., and Ozmert, E., "Rapid improvement of retinal and iris neovascularization after a single intravitreal bevacizumab injection in a patient with central retinal vein occlusion and neovascular glaucoma," *Int Ophthalmol*, 28(1), 59-61.2008.
- [21] Astam, N., Batioğlu, F., and Ozmert, E., "Short-term efficacy of intravitreal bevacizumab for the treatment of macular edema due to diabetic retinopathy and retinal vein occlusion," *Int Ophthalmol*, 29(5), 343-8.2009.
- [22] Natarajan, S., "Managing patients with retinal vein occlusions: is there any real step forward?," *Indian J Ophthalmol*, 60(4), 251-4.2012.
- [23] Hayreh, S.S., "Ocular vascular occlusive disorders: natural history of visual outcome," *Prog Retin Eye Res*, 41, 1-25. 2014.
- [24] Hoeh, A.E., Ach, T., Schaal, K.B., et al, "Long-term follow-up of OCT-guided bevacizumab treatment of macular edema due to retinal vein occlusion," *Graefes Arch Clin Exp Ophthalmol*, 247(12), 1635-41.2009.
- [25] Pfister, M., Rothweiler, F., Michaelis, M., et al, "Correlation of inflammatory and proangiogenic cytokines from undiluted vitreous samples with spectral domain OCT scans, in untreated branch retinal vein occlusion," *Clin Ophthalmol*, 7, 1061-7.2013.
- [26] Manousaridis, K., and Talks, J., "Macular ischaemia: a contraindication for anti-VEGF treatment in retinal vascular disease?," *Br J Ophthalmol*, 96(2), 179-84.2012.
- [27] Romano, M.R., Biagioni, F., Besozzi, G., et al, "Effects of bevacizumab on neuronal viability of retinal ganglion cells in rats," *Brain Res*, 1478, 55-63. 2012.
- [28] Higashide, T., Murotani, E., Saito, Y., et al, "Adverse events associated with intraocular injections of bevacizumab in eyes with neovascular glaucoma," *Graefes Arch Clin Exp Ophthalmol*, 250(4), 603-10.2012
- [29] Pacella, E., La Torre, G., Impallara, D., et al., "Efficacy and safety of the intravitreal treatment of Diabetic Macular Edema with Pegaptanib: a 12-month follow-up," *Clin Ter*, 164 (2), 1-3. 2013.