Romanian Journal of Ophthalmology, Volume 60, Issue 2, April-June 2016. pp:90-95

GENERAL ARTICLE

"Off-label" use of intravitreal bevacizumab in non-ischemic macular edema secondary to retinal vein obstructions

Dascalu Ana Maria, Popa-Cherecheanu Alina, Popa-Cherecheanu Matei, Nica Adriana, Serban Dragos
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
Department of Ophthalmology, University Emergency Hospital Bucharest, Romania

Correspondence to: Alina Popa-Cherecheanu, MD, PhD,
Department of Ophthalmology, University Emergency Hospital Bucharest, Romania
169 Spl. Independentei Street, District 5, Bucharest, Romania,
Mobile phone: +4073 2507047, E-mail: alina_cherecheanu@yahoo.com

Accepted: April 15, 2016

Abstract

Objective. To evaluate the safety and efficacy of intravitreal Bevacizumab in treatment of non-ischemic macular edema secondary to retinal vein obstruction (RVO).

Materials and Methods. A 2-year-retrospective study was performed on 26 patients hospitalized for non-ischemic macular edema secondary to RVO. All the patients underwent a complete ophthalmologic exam, with best corrected visual acuity (BCVA) testing, fundus photography, fluorescein angiography (FA) and macular thickness measurement by optical coherence tomography (OCT). Reevaluation was performed monthly for VA, OCT, and ophthalmoscopy and, at every 3 months, by FA. A standard protocol of 0.05 ml intravitreal Bevacizumab injection was applied. Further administrations were performed according to clinical evolution.

Results. The medium follow–up period was of 9,7 months (6-20 months). There were no significant complications following the procedure. The number of intravitreal Bevacizumab injections varied from 2-5/ patient. All the patients experienced an improvement in VA and a significant regression of macular edema. The smallest number of intravitreal Bevacizumab injections and the best visual prognosis were observed in cases with branch retinal vein obstruction (BRVO) and early presentation ($p<0.05$).

Conclusions. As a pathogenic therapy, intravitreal Bevacizumab is a safe, repeatable procedure and it may be considered an effective and lasting treatment for non-ischemic macular edema secondary to RVO. Intravitreal Bevacizumab should be included in the therapeutic protocol of RVO, both for early and delayed presentations.

Keywords: intravitreal, Bevacizumab, retinal vein obstruction, macular edema

Abbreviations: RVO = retinal vein obstruction, BRVO = branch retinal vein obstruction, CRVO = central retinal branch obstruction, BCVA = best corrected visual acuity, FA = fluorescein angiography, OCT = optical coherence tomography

Introduction

Retinal vein obstruction (RVO) is a major cause of visual impairment in patients over 50 years old and secondary macular edema is a frequent associated condition with an immediate impact upon the visual acuity. Until the past years, grid laser photocoagulation has been the standard of care for treatment in RVO. However, poor vision persists despite the photocoagulation treatment

Romanian Society of Ophthalmology
© 2016

in many patients, and its use is not recommended until 3 months after the development of RVO [1]. The pathogenesis of this condition is thought to involve both the retinal vein compression and the damage to the vessel wall, possibly leading to thrombus formation at sites in which retinal arterioles cross retinal veins. As elevated intraocular levels of VEGF have been demonstrated in patients with retinal vein occlusions, there is a strong basis for the hypothesis that anti-VEGF agents may be benefic [2,3].

Purpose

The present study aims to evaluate the safety and efficacy of "off label" use of intravitreal Bevacizumab in the treatment of non-ischemic macular edema secondary to RVO.

Materials and methods

A 2-year-retrospective study was performed on 26 patients admitted for retinal vein obstruction and treated with intravitreal Bevacizumab. All the patients underwent a complete ophthalmologic exam, best corrected visual acuity (BCVA) testing, fundus photography, fluorescein angiography (FA, VisuCam Zeiss) and central macular thickness measurement (Cirrus HD-OCT, Zeiss). A standard protocol of 0.05 ml intravitreal Bevacizumab injection was applied, using topical anesthesia, under strict antiseptic rules in the Operation Room. Further administrations were performed according to the clinical evolution, but not earlier than one month after the previous injection. The efficacy of the treatment was assessed in terms of VA, central macular thickness measured by OCT and decreased leakage in angiofluorography (FA).

Results

The medium follow–up period was of 9,7 months (6-20 months). The mean age was of 62,3 years, with limits between 42 and 78 years. Most of the patients presented associated risk factors for vein thrombosis, such as: arterial hypertension (18 cases), ischemic coronary disease (13 cases), diabetes (6) and antiphospholipid syndrome (2 cases). Only 2 out of the 26 patients had no associated pathology. Out of the 26 patients, 9 presented with central retinal vein obstruction (CRVO) and 17 with branch retinal vein obstruction (BRVO). The therapy was well accepted by the patients and no significant complications following the procedure were reported. The number of intravitreal Bevacizumab injections varied from 2-5/ patient.

According to the time elapsed from the acute event to the initiation of the anti-VEGF therapy, 2 groups were described:

- Group A: early presentation (up to 3 months): 11 patients (4 with CRVO and 7 with BRVO)

- Group B: delayed presentation (> 3 months): 15 patients (5 with CRVO and 10 with BRVO)

The evolution of BCVA, macular thickness measured by OCT and leakage (FA) before and after treatment were analyzed separately for the 2 groups. The comparative results are presented in Table 1:

Table 1. Initial and final BCVA, central macular thickness and FA aspects in patients with early presentation (group A) vs. delayed presentation (group B)

	Initial BVCA	Final BVCA	Macular thickness (OCT)	FA/ Observations
Group A Early presentation	0.25 (0.5-0.025)	0.52 (0.12-1)	Initial: 486 +/ -123 µm Final: 295 ± 136 µm	✓ diminished exudation and retinal edema ✓ no retinal neovessels or secondary glaucoma during follow-up period
Group B Delayed presentation	0.09 (light perception-0.1)	0.12 (0.02-0.25)	Initial: 687 +/ - 215 µm Final: 423+/ -143 µm	✓ decreased retinal neovascularization and macular leakage ✓ no angle neovessels or neovascular glaucoma during follow-up period

In order to assess the anti-VEGF therapeutic efficacy, the results underwent statistical analysis (Wilcoxon signed-rank test, t-test, SPSS).

One of the parameters investigated in the present study was BCVA. The main goal in retinal vein thrombosis is the restoration of a good visual acuity, which allows the patients to continue a normal daily life. The patient immediately perceives any change, thus it is a good subjective evaluation of the therapeutic efficacy. In Group A, BCVA increased from 0.25 to 0.52 after treatment. The statistical analysis proved that there was a significant improvement of BCVA after the anti VEGF therapy (Z=-2,940, p =0,003).

© 2016

Table 2. Wilcoxon Signed Ranks Test applied to pre and post-therapeutic BCVA in group A

	N	Medium	Standard deviation	Minimum	Maximum
Initial BCVA	11	.2500	.07759	.11	.39
Post therapy BVCA	11	.5200	.09644	.38	.68

		N	Mean Rank	Sum of Ranks
Post therapy BVCA - Initial BCVA	Negative Ranks	0[a]	.00	.00
	Positive Ranks	11[b]	6.00	66.00
	Ties	0[c]		
	Total	11		

a. Post therapy BCVA < Initial BCVA

b. Post therapy BCVA > Initial BCVA

c. Post therapy BCVA = Initial BCVA

Statistical test[b]

	Post therapy BCVA - Initial BCVA
Z	-2.940[a]
Asymp. Sig. (2-tailed)	.003

a. Based on negative ranks.

b. Wilcoxon Signed Ranks Test

For group B, BVCA increased from 0.09 before treatment to 0.12. The improvement was also statistically significant (Z=-2,789, p=0,005). However, BCVA remained below 0.1 in the majority of the cases.

The statistical analysis showed significant differences between the 2 groups in terms of recovery of the BCVA. The vision was much better improved in patients with early presentation (U=6, p=0,001, Z=-3,976). This observation can be explained by the fact that after chronic ischemic alterations and neovessels appears, the anti VEGF therapy increases BCVA, but the restoration of a useful vision is less probable.

Table 3. Wilcoxon Signed Ranks Test applied to compare the visual improvement between group A and group B after intravitreal Bevacizumab therapy

	N	Mean	Standard deviation	Minimum	Maximum
Post-therapy BCVA	26	.2850	.21971	.00	.68
Moment of presentation (<3 months=1; after 3 months=2)	26	1.58	.504	1	2

Ranks

	Moment of presentation (<3 months=1; after 3 months=2)	N	Mean Rank	Sum of Ranks
Post-therapy BCVA	1	11	21.00	231.00
	2	15	8.00	120.00
	Total	26		

Statistical Test[b]

	Post-therapy BCVA
Mann-Whitney U	.000
Wilcoxon W	120.000
Z	-4.286
Asymp. Sig. (2-tailed)	.000
Exact Sig. [2*(1-tailed Sig.)]	.000[a]

a. Not corrected for ties.

b. Grouping Variable: Moment of presentation (<3 months=1; after 3 months=2)

Romanian Society of Ophthalmology
© 2016

The final BCVA was better for patients with BRVO as opposed to CRVO ($p<0.05$) inside every group.

Central retinal thickness measured by OCT was a non-invazive repeatable test that proved to be very important in long-term follow-up of the patient with retinal thrombosis. It correlated well with visual acuity but also with pathogenic processes that developed locally in the ischemic retina and led to leakage and microvascularization abnormalities. Clinical studies showed a direct relation between the levels of VEGF-A in vitreous fluids and SD-OCT aspects in patients with RVO [2].

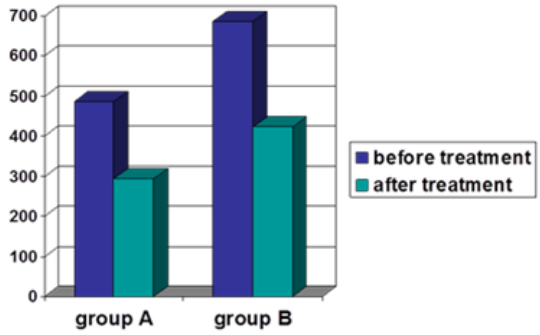


Fig. 1 Central macular thickness (Stratus - OCT Zeiss) before and after anti-VEGF therapy

A statistically significant decrease of the central macular thickness was noticed ($p<0.05$) in both study groups. What should also be mentioned is that in group A the value was close to normal, a slight retinal atrophy being observed in some cases after the remission of the edema. Moreover, some degrees of macular edema usually persisted and could be well correlated with areas of vascular abnormalities and leakage observed on FA, in group B.

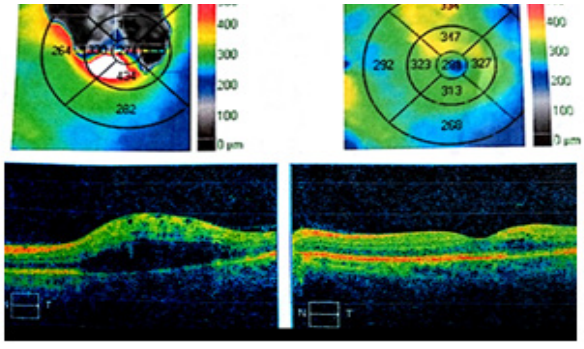


Fig. 2 Supramacular retinal branch vein obstruction; OCT Macular change analysis: significant diminished macular edema after treatment

Fundus photography and FA were important tools both for diagnosis and for follow-up. FA differentiated between the ischemic and non-ischemic form of retinal vein thrombosis and showed the extension of the affected territory, leakage, and vessel abnormalities (arterio-venous shunts, microaneurysms, duplications, and intraretinal neovessels). The pathologic features on initial and final FA are presented in Table 4.

Table 4. FA aspects in Group A and Group B

	Group A		Group B	
	Pre treatment	Post treatment	Pre treatment	Post treatment
Retinal edema	+++	+	+	+/-
Exudates, hemorrhages	+++	+	+	-
Neovessels	_	-	+	+/-
Secondary neovascular glaucoma	-	-	-	-

Anti VEGF therapy proved to be associated with decreased leakage and neovascularization, thus reducing macular edema and preventing a severe complication of retinal vein thrombosis: secondary neovascular glaucoma (Fig. 3 (a,b,c), Fig. 4 (a,b,c,d).

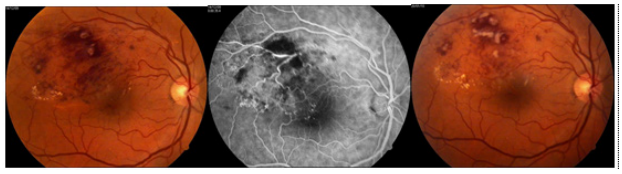
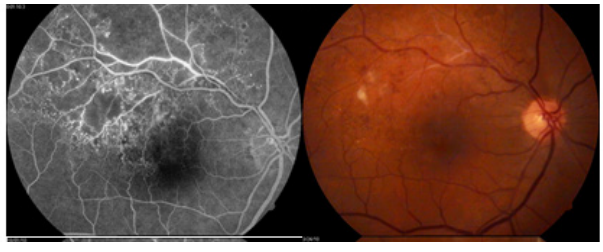


Fig. 3 a) early presentation of BRVO with important macular edema, retinal hemorrhage and hard exudates; b) FA aspect at admission: leakage, microaneurysms and arterio-venous shunts; hypofluorescence areas due to mask effect of retinal hemorrhages; c) aspect after intravitreal Bevacizumab injection, with significant decreased macular edema



© 2016

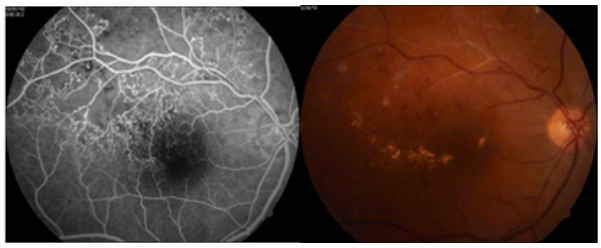


Fig. 4 Partial decrease of leakage and abnormal vessel formation in a case of BRVO with delayed presentation after intravitreal Bevacizumab: a) initial aspect at FA; b) initial aspect at fundus photography c) FA after 3 intravitreal Bevacizumab injections; d) fundus photography after 3 intravitreal Bevacizumab injections

Discussions

Secondary macular edema related to RVO is associated with significant impairment in vision-related quality of life. The main directions of therapy are laser photocoagulation, anti-VeGF agents, and intravitreal corticosteroids administration, but there is no consensus regarding the standard protocol to be used in the therapeutic management of this condition.

Bevacizumab is a very effective anti-VEGF and intravitreal administration, perfectly justified as a pathogenic therapy in cases with RVO [1-4]. The early treatment with intravitreal Bevacizumab was associated with a greater improvement in the visual acuity compared with the delayed treatment [5]. The effect proved more important than of grid laser photocoagulation and longer lasting and associated with fewer side effects than intravitreal corticosteroids [5-7]. Russo et al. found a change of +15.5 letters in Bevacizumab treated patients with BCVA and +10 letters in grid laser photocoagulation ($p<0.05$), achieved by a mean number of 1.7 intravitreal injections of Bevacizumab and 1.5 grid applications [8].

Intravitreal agents have replaced the observation in macular edema in central (CRVO) and grid laser photocoagulation in branch retinal vein occlusion (BRVO). No significant differences were found between the Bevacizumab and ranibizumab therapeutic effect [9-11]. Epstein and colleagues found that CRVO patients treated with 1.25 mg Bevacizumab at every 6 weeks from baseline gained +16.1 letters, compared to +4.6 letters in those treated with sham injections followed by Bevacizumab ($p<0.05$). The percentage of BCVA gain of more than 15 letters was 60% (Bevacizumab) vs. 33.3% (sham/Bevacizumab), respectively ($p<0.05$) [9,12].

The present study showed that intravitreal Bevacizumab was a good treatment option for non-ischemic macular edema secondary to RVO. The early presentation and BRVO were associated with the best visual prognosis, and the therapeutic effect was statistically significant in all cases. However, the limited number of patients and the follow-up period could not allow the drawing of conclusions regarding the frequency of re-treating and the final visual outcome. Further studies, on a long-term follow-up and a large number of cases are still needed. Most of the patients (24 out of 26), also had associated risk factors for thrombosis (diabetes, cardio-vascular diseases). It is reasonable to think that the outcome and the probability of repeating the thrombotic event depended on the adequate treatment of the associated general pathology.

In a review of literature, the most important complications associated with intravitreal Bevacizumab were endophthalmitis and systemic vascular adverse effects, like cerebral infarction, elevated systolic blood pressure, facial skin redness, itchy diffuse rash [13-15]. In the present study, 2 side effects were reported: a skin rash, which resolved spontaneously in less than 24 hours and one patient who developed a transient cerebral accident 4 weeks after the intravitreal injection. However, the role of intravitreal Bevacizumab in the incidence of adverse events remains unclear, taking into account the pre-existing risk factors encountered in patients with RVO.

Conclusions

As a pathogenic therapy, intravitreal Bevacizumab is a safe, repeatable procedure and it may be considered an effective and lasting treatment for macular edema, due to the leakage after retinal vein occlusion. It also proved to be useful both for preventing and for treating retinal neovascularization in a short and medium term follow-up. Factors associated with good recovery of VA were the following: early presentation, branch retinal vein obstruction, non-ischemic macular edema. Though the treatment was most

Romanian Society of Ophthalmology
© 2016

effective in the early presentation, patients with delayed presentation also experienced a favorable evolution and the regression of neovessels was a strong argument for the prevention of secondary neovascular glaucoma in these cases.

Intravitreal Bevacizumab should be included in the therapeutic protocol of retinal vein obstruction, both for early and delayed presentations. Further studies are still necessary for long-term evolution.

Disclosure
None.

References

1. Glanville J, Patterson J, McCool R, Ferreira A, Gairy K, Pearce I. Efficacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review. BMC Ophthalmol. 2014 Jan 21; 14:7. doi: 10.1186/1471-2415-14-7.
2. Mitry D, Bunce C, Charteris D. Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein occlusion. Cochrane Database Syst Rev. 2013 Jan 31; 1:CD009510. doi: 10.1002/14651858.CD009510.pub2.
3. Pfister M, Rothweiler F, Michaelis M, Cinatl J Jr, Schubert R, Koch FH, Koss MJ. Correlation of inflammatory and proangiogenic cytokines from undiluted vitreous samples with spectral domain OCT scans, in untreated branch retinal vein occlusion. Clin Ophthalmol. 2013; 7:1061–1067.
4. Vascular Endothelial Growth Factor Promotes Progressive Retinal Nonperfusion in Patients with Retinal Vein Occlusion. Ophthalmology. 2013; 120(4):795–802.
5. Ehlers JP, Decroos FC, Fekrat S. Intravitreal Bevacizumab for macular edema secondary to branch retinal vein occlusion. Retina. 2011 Oct; 31(9):1856-62. doi: 10.1097/IAE.0b013e31820d59a5.
6. Yeh S, Kim SJ, Ho AC, Schoenberger SD, Bakri SJ, Ehlers JP, Thorne JE. Therapies for macular edema associated with central retinal vein occlusion: a report by the American Academy of Ophthalmology. Ophthalmology. 2015 Apr; 122(4):769-78. doi: 10.1016/j.ophtha.2014.10.013.
7. Kriechbaum K, Prager S, Mylonas C, Scholda C, Rainer G, Funk M, Kundi M, Schmidt-Erfurth U. Intravitreal Bevacizumab (Avastin) versus triamcinolone (Volon A) for treatment of diabetic macular edema: one-year results. Eye. 2014; 28,9–16. doi:10.1038/eye.2013.242.
8. Russo V, Barone A, Conte E, Prascina F, Stella A, Noci ND. Bevacizumab compared with macular laser grid photocoagulation for cystoid macular edema in branch retinal vein occlusion. Retina. 2009; 29(4):511–515. doi: 10.1097/IAE.0b013e318195ca65.
9. Pielen A, Feltgen N, Isserstedt C, Callizo J, Junker B, Schmucker C. Efficacy and Safety of Intravitreal Therapy in Macular Edema Due to Branch and Central Retinal Vein Occlusion: a Systematic Review. PLoS ONE 2013; 8(10):e78538. doi:10.1 1.
10. Moradian S, Faghihi H, Sadeghi B, Piri N, Ahmadieh H, Soheilian M, Dehghan MH, Azarmina M, Esfahani MR. Intravitreal Bevacizumab vs. sham treatment in acute branch retinal vein occlusion with macular edema: results at 3 months (Report 1). Graefes Arch Clin Exp Ophthalmol. 2011; 249(2):193–200. doi: 10.1007/s00417-010-1440-8.
11. Narayanan R, Panchal B, Das T, Chhablani J, Jalali S, Ali H. A randomised, double-masked, controlled study of the efficacy and safety of intravitreal Bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1. Br J Ophthalmol. 2015; 99:954-959 doi:10.1136/bjophthalmol-2014-306543.
12. Epstein DL, Algvere PV, Von Wendt G, Seregard S, Kvanta A. Benefit from Bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. Ophthalmology. 2012; 119:2587–2591. doi: 10.1016/j.ophtha.2012.06.037.
13. Shima C, Sakaguchi H, Gomi F, Kamei Y, Ikuno Y, Oshima Y, Sawa M et col. Complications in patients after intravitreal injection of Bevacizumab. Acta Ophthalmologica. 2008; 86(4):372–376.
14. Inman ZD, Anderson NG. Incidence of endophthalmitis after intravitreal injection of antivascular endothelial growth factor medications using topical lidocaine gel anesthesia. Retina. 2011; 31:669–72.
15. Johnson D, Hollands H, Hollands S et al. Incidence and characteristics of acute intraocular inflammation after intravitreal injection of Bevacizumab: a retrospective cohort study. Can J Ophthalmol. 2010; 45:239–42.