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Joaquin Marticorena, Mario R Romano, Heinrich Heimann, Theodore Stappler, Kurshid S Gibran, et al.. Intravitreal bevacizumab for retinal vein occlusion and early growth of epiretinal membrane: a possible secondary effect?. British Journal of Ophthalmology, 2010, 95 (3), pp.391. 10.1136/bjo.2009.177287 . hal-00567049

HAL Id: hal-00567049

<https://hal.science/hal-00567049>

Submitted on 18 Feb 2011

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Intravitreal bevacizumab for retinal vein occlusion and early growth of epiretinal membrane: a possible secondary effect?

Authors:

Joaquin Marticorena M.D., Ph.D.,¹ Mario R Romano M.D.,² Heinrich Heimann M.D.,² Theodore Stappler M.D.,² Kurshid Gibran M.D.,³ Carl Groenewald M.D.,² Ian Pearce M.D.,¹ David Wong M.D.⁴

Affiliation:

1. Instituto Tecnológico de Oftalmología, Santiago de Compostela, Spain.
2. Saint Paul's Eye Unit. Royal Liverpool University Hospital, Liverpool. United Kingdom.
3. Department of Ophthalmology, UTMB, Galveston, TX, USA.
4. Faculty of Medicine Li Ka Shing, University of Hong Kong. Hong Kong SAR, China.

Keywords: vein occlusion, epiretinal membrane, ischaemia.

This study was performed at Saint Paul's Eye Unit, Royal Liverpool University Hospital. Liverpool. United Kingdom.

No grants or funds have been involved in the development of this study.

This paper has not been previously presented in any congress or presented as an abstract. None of the authors have any proprietary interest related with topics contents in this article. This study has not been presented before at any meeting or congress.

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Competing interest: None declared.

Corresponding author and reprint requests: Dr Joaquin Marticorena. Instituto Tecnológico de Oftalmología, Santiago de Compostela, Spain. E-mail: jmarticorena@gmail.com

ABSTRACT

Aims: To report the early development of epiretinal membranes (ERM) in eyes with retinal vein occlusions (RVO) treated with intravitreal bevacizumab and to describe possible mechanisms that may be involved in the growth and contraction of these lesions.

Methods: Retrospective and interventional study that included 25 eyes of 25 patients with RVO (16 eyes with central retinal vein occlusion and 9 eyes with branch retinal vein occlusion). After an initial 2.5mg/0.1ml intravitreal bevacizumab injection all patients were followed every 6 weeks. Retreatments were based in visual acuity and optical coherence tomography findings.

Results: Twenty-five eyes were treated with bevacizumab and followed for 8.3 months (range, 4.5 – 13.5). Four eyes developed an ERM within 6 -7 weeks after the administration of bevacizumab. ERM was not associated with further deterioration of visual acuity or metamorphopsia in these patients. A rebound of macular oedema was observed in 1 patient with ERM and in 2 other patients. No other side effects were observed.

Conclusions: Intravitreal bevacizumab may be associated with an early growth of ERM in eyes with RVO, although a causative relationship cannot be established, future randomized clinical trials are necessary to determine the efficacy and safety profile of this novel therapy.

Introduction

Retinal vein occlusion (RVO) is a vascular disease that can be subdivided into central retinal vein occlusions (CRVO) and branch retinal vein occlusions (BRVO). Both diseases are associated with an up-regulation of vascular endothelial growth factor (VEGF) mRNA and with increased intraocular levels of VEGF, especially in those where neovascularization is present.¹ The presence of macular oedema in patients with RVO has also been associated with higher levels of VEGF and retinal ischemia. Inhibiting the effect VEGF would be a rationale therapy to reduce macular oedema, retinal ischemia and to prevent neovascularization in eyes with RVO. Bevacizumab (Avastin, Genentech, Inc, San Francisco, California) is a full-length humanized monoclonal non-selective antibody against VEGF approved by the Food and Drug Administration for the treatment of metastatic colorectal cancer in combination with chemotherapy. Since the first report of a patient with CRVO treated with intravitreal bevacizumab by Rosenfeld et al,² several studies have described functional and anatomic improvement in patients affected with RVO treated with this anti-VEGF therapy.³⁻⁶ This novel therapy seems to be well tolerated even after numerous retreatments. However, a rebound of macular oedema associated with deterioration of visual acuity has been described and an increase of retinal ischaemia in a patient with CRVO has been reported in relation to the administration of intravitreal bevacizumab.^{7,8} The purpose of this study is to describe the early onset of secondary epiretinal membrane (ERM) in eyes with RVO treated with intravitreal bevacizumab.

Material and Methods

A retrospective, interventional and non-comparative case series study was conducted with the approval of the Institutional Ethics Committee. Patients with CRVO or BRVO were offered to be treated with an intravitreal injection of bevacizumab. In all cases a signed informed consent was obtained. Evaluation with best corrected visual acuity (BCVA) with Snellen charts, non-contact intraocular pressure (IOP) measurement, slit lamp examination of the anterior segment, exploration of the fundus by biomicroscopy and macular thickness measurement using optical coherence tomography (OCT; OCT Stratus, Carl Zeiss Meditec, Dublin, California) was done at baseline and thereafter approximately every 6 weeks. In 8 patients a fluorescein angiography was performed at baseline. All patients with previous therapy for RVO (i.e. laser photocoagulation, intravitreal triamcinolone) and/or intraocular surgery within the previous 6 months, patients with history of uveitis or other pathologies that may affect the macula (i.e. diabetic retinopathy) were excluded from this study.

Each dose of 2.5mg/0.1ml bevacizumab was prepared in the pharmacy of the hospital under sterile conditions and administered as an intravitreal injection in theatre. All patients received topical chloramphenicol 0.5% four times a day for 3 days after the injection.

A positive response to intravitreal bevacizumab was normally assumed if there was an increase in BCVA of 2 or more Snellen lines together with a decrease equal or greater than 100 μ m of central macular thickness. Retreatment criteria was at discretion of the specialist, but generally it was indicated if: (1) after an initial positive response there was persistent intra or subretinal fluid, (2) after an initial positive response there was a decrease of 2 or more BCVA lines with or without increase of central macular thickness (3) absence of positive response to the initial injection. In those patients that showed no positive response after 2 consecutive treatments, the administration of further bevacizumab injections was discarded.

The diagnosis of ERM was established by biomicroscopy and by an OCT image showing the presence of a highly reflective layer on the inner retinal surface at the macular area.

For the statistical analysis, BCVA was converted into logMAR units. All continuous variables are expressed as mean \pm standard deviation. Serial changes in BCVA and macular thickness were compared with Wilcoxon paired test. All data were analyzed with SPSS 13.0 (SPSS Inc., Chicago, IL). A *P* value < 0.05 was considered to be significant.

Results

Twenty-five eyes of 25 patients, 14 male and 11 female, were included in this study. In 16 eyes (64%) the diagnosis of CRVO was done, while 9 eyes (36%) were catalogued as having BRVO. Mean age at baseline was 64 ± 14 years (range, 38 – 84).

Before intravitreal bevacizumab, in the group of patients with BRVO, 2 eyes had been treated with argon laser macular grid photocoagulation, 1 eye with intravitreal triamcinolone acetonide (IVTA) and 2 eyes with IVTA and grid laser. In the group of patients with CRVO, 2 of them had 1 previous IVTA injection and 1 patient received argon laser panretinal photocoagulation. All these treatments were administered at least 6 months before the bevacizumab injection.

Patients were followed for 8.3 ± 3.3 months (range, 4.5 – 13.5). The mean time period between the beginning of the symptoms related to RVO and the administration of bevacizumab was 15 ± 24 months (range, 0.5 – 97.5). Eleven patients were treated with a single initial injection, 8 patients with 2 injections and 6 patients with 3 injections, resulting in an average of 1.8 injections per eye.

At baseline, mean BCVA was 1.00 ± 0.57 logMAR and an improvement in BCVA

was observed throughout the follow-up. The increase in BCVA was statistically significant compared with baseline at week-6, week-12, week-30, week-36 and week-54 visits (Table 1).

Mean initial central macular thickness measured with OCT was 463 ± 204 μ m and a statistically significant decreased was observed at week-6, week-12, week-24, week-30, week-36 and week-54.

In the subgroup analysis, patients with BRVO showed an initial mean BCVA of 0.67 ± 0.38 logMAR and central retinal thickness of 347 ± 133 μ m. During follow-up, there were no statistically significant differences in these two variables compared with baseline. Patients with CRVO showed an initial mean BCVA of 1.18 ± 0.58 logMAR and a significant increase was observed after 6 weeks ($p < 0.01$), 12 weeks ($p = 0.01$), 30 weeks ($p = 0.02$) and 36 weeks ($p = 0.02$). Initial mean central macular thickness was 529 ± 211 μ m and a statistically significant decrease was observed after 6 weeks ($p = 0.03$), 24 weeks ($p = 0.02$), 30 weeks ($p = 0.02$) and 36 weeks ($p = 0.02$). Baseline BCVA and central retinal thickness were statistically different between BRVO and CRVO subgroups and no further comparisons were done between them.

Four patients (3 with CRVO and 1 with BRVO) developed an ERM following the administration of intravitreal bevacizumab (Figures 1 – 3). Characteristics of these patients are described in Table 2.

Increase of central retinal thickness and deterioration of BCVA in 1 or more lines compared with baseline occurred in 3 cases (12%), 1 patient with BRVO and 2 patients with CRVO. This rebound was detected after 6 to 18 weeks from previous bevacizumab injection. One of these patients did not receive further therapy and no anatomical or functional improvement was observed during the following 12 weeks. The second patient showed an improvement of BCVA and a decrease in central macular thickness

compared with baseline after being retreated. The third patient with rebound developed an ERM and corresponds to Case 1 of Table 2.

No other ocular or systemic complications related to the use of intravitreal bevacizumab were observed during this study.

Discussion

The results of the present study are congruent with several previous reports in which repeated intravitreal bevacizumab injections have been associated with short-term anatomical and functional improvement in patients with RVO, needing repeated injections to maintain this transient benefit in most of the patients.³⁻⁶ Subgroup analysis showed significant improvement of BCVA and decrease of macular oedema in patients with CRVO treated with bevacizumab, but not in those with BRVO. We believe that the lack of benefit observed in the BRVO group may be related to the sample size.

Recurrence of macular oedema appears to be a frequent situation despite the use of fixed initial retreatments and high rate of reinjections of bevacizumab. In our series, we observed not only recurrence of macular oedema, but also rebound of cystoid macular oedema with deterioration of visual acuity compared with baseline in 3 patients. In 2 of these eyes, retreatment with bevacizumab produced a new decrease in central macular thickness due to reabsorption of macular oedema and increase in BCVA.

Previous reports of intravitreal bevacizumab for RVO have described the reabsorption of macular oedema by measuring the central macular thickness with OCT, but few details regarding the qualitative changes of the macula have been given. It is known that OCT is a very useful tool for the diagnosis of ERM especially in cases where macular edema and intraretinal hemorrhages may difficult the diagnosis by biomicroscopy. In our study, an incidence of 16% of secondary ERM was observed,

similar to the 16.1% observed by the Blue Mountains Study in eyes with RVO.⁹ Interestingly, there is no description in the literature of ERM growth in patients with RVO treated with bevacizumab despite the numerous studies recently published. On possible explanation to this situation may be that most of these studies are centered in the description of quantitative changes of central macular thickness measured with OCT, but few data is given about the qualitative changes of the macula during follow-up. Due to the characteristics of our study it is difficult to determine a cause-effect relationship between intravitreal bevacizumab and early development of secondary ERM, but there are some elements that allows us to establish this possibility. First, in an early report done by Wise G,¹⁰ the development of “preretinal folds” occurred between 6 and 12 months after the diagnosis of RVO. These folds are not other than the tractional forces of the contracted ERM on the retinal surface. The growth and contraction ERM is though to be a slow process, but in our study ERM rapidly appeared 6-7 weeks after the injection of bevacizumab in eyes with RVO diagnosed 5.5 to 12.5 months before. Another case with history of 44.5 months of CRVO, developed a premacular membrane only 7 weeks after a second injection of bevacizumab, suggesting that this treatment might be related with this change in the evolution of the disease and beginning of premacular proliferation. But, how can bevacizumab participate in the development of ERM in eyes with RVO? The administration of an anti-VEGF therapy does not only block the pro-angiogenic stimulus of VEGF, it changes the relation, expression and activity of numerous cytokines, growth factors and mediators present in the retinal tissue, retinal vessels and retinal surface. A rise in the levels of VEGF produces an increase in nitric oxide (NO) production by endothelial cells.¹¹ NO is involved in controlling retinal blood flow during hypoxia and constitutes a main pathway to stimulate endothelial cell proliferation, migration, release of proteases and increase in capillary permeability.¹²⁻¹⁵ In an experimental model, Donati et al observed that a decrease in NO production causes

an arteriolar constriction in eyes with BRVO, contributing to maintain the hypoxia.¹⁶ It has been proposed that anti-VEGF therapy could reduce the capacity of the endothelium to produce NO.¹¹ Therefore, despite the anti-oedematous and anti-angiogenic role of bevacizumab, it could also produce an increase in retinal ischemia by reducing NO production. Clinically, the transformation of a non-ischaemic CRVO into a ischaemic CRVO after intravitreal bevacizumab have been recently described.⁸ Apart from VEGF there are some other factors like platelet-derived growth factor A and tumour necrosis factor-alfa that participate in the growth of ERMs.¹⁷⁻¹⁹ An increase of such factors, as a consequence of persistent ischemia, could explain the development of ERM in patients with RVO treated with bevacizumab. In our study, visual acuity remained stable in 2 of the patients with ERM after bevacizumab compared with baseline, while in the other 2 patients there was an improvement of vision. Even when ERM can limit visual recovery, vitrectomy and peeling of the membrane was not indicated since ERM was not associated with further deterioration of visual acuity or metamorphopsia.

It is well known that in ischemic retinopathies VEGF is up-regulated while pigment epithelium-derived factor (PEDF), an angiostatic and neurothrophic factor, is decreased.²⁰ Therefore, the administration of an anti-VEGF agent produces an imbalance towards the effect of PEDF. In addition, PEDF production by retinal glial cells is increased under a marked hypoxia environment.²¹ Enhanced expression and location of PEDF, as well as its capability of being stimulated by transforming growing factor beta (TGF- β), has been observed in progressive fibrotic pathologies.²² It suggests that a relative increase in PEDF after intravitreal bevacizumab may promote fibrotic changes of ERM in eyes with retinal ischemia. Hypoxia can also promote the expression of TGF- β in Muller cells,²³ and consequently the presence of connective tissue growth factor (CTGF), an important mediator of retinal fibrosis and development of ERM.²⁴ In other tissues

VEGF has shown to inhibit the expression of CTGF in a complex mechanism in which is also involved TGF- β .²⁵ We may hypothesize that the blockage of VEGF through bevacizumab may increase the relative effect of factors such as PEDF and CTGF. This may produce a rapid development of the fibrotic component of an early ERM. Fibrosis, contraction and wrinkling of the ERM make more evident the presence of the epimacular tissue, facilitating the diagnosis of previously undetected lesions.

In conclusion, bevacizumab appears as a symptomatic treatment for vaso-occlusive diseases since recurrence of macular oedema is a frequent situation, even after repeated injections. The early development of secondary ERM in eyes with RVO may constitute a secondary effect of intravitreal bevacizumab considering the time effect relationship observed in the present study and the theoretical basis that can explain this phenomenon. We describe different mechanism that may promote the growth ERM in eyes with RVO, as well as an increase in fibrosis and secondary contraction of epimacular tissue after intravitreal bevacizumab. Although intravitreal bevacizumab is emerging as one of the possible treatments in retinal venous disease, we encourage the cautious administration of this therapy until randomized masked clinical trials determine the safety and efficacy of this treatment.

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Legends

Figure 1. Case 1. (A) Baseline horizontal OCT scan showing cystoid macular edema (central retinal thickness of 619 μ m). At that moment BCVA was 20/120. (B) Thirty-six weeks after initial treatment and 7 weeks after a second bevacizumab injection, BCVA is 20/30 and central retinal thickness 328 μ m. The horizontal OCT image shows a very fine hyper reflective layer on the inner surface of the retina at both sides of the fovea compatible with early ERM. (C) Rebound of cystoid macular edema 15 weeks after last bevacizumab injection. BCVA has decreased to 20/200. It is possible to observe in the horizontal OCT an increase in the reflectivity of the ERM, now forming small bridges of tissue on the inner surface of the retina. A third injection of bevacizumab was

administrated. **(D)** Twelve weeks after last therapy, the OCT shows reabsorption of macular edema and central retina thickness has decreased to 253 μm and BCVA improved to 20/80, however there is persistence of ERM.

Figure 2. Case 2. Right eye of a patient with initial BCVA of 20/200 and central macular thickness of 627 μm . **(A)** horizontal OCT scan with cystoid macular edema and foveolar serous detachment. **(B)** Six weeks after intravitreal bevacizumab, most of the intraretinal and subretinal fluid has reabsorbed. At the inner surface of the nasal retina is possible to observe a very fine layer of hyper reflective tissue compatible with early ERM. At that moment central retinal thickness was 243 μm and BCVA 20/40. Case 3. **(C)** Initial OCT horizontal scan showing cystoid edema at the foveal area. Baseline central macular thickness was 320 μm and BCVA 20/120. **(D)** Six weeks after bevacizumab injection there is a hyper reflective layer at the inner surface of the retina adjacent to the fovea. Central macular thickness was to 311 μm and BCVA was 20/120. There were no changes in the appearance of the retina during the following visits.

Figure 3. Case 4. **(A)** Baseline OCT scan shows the presence of cystoid macular edema and central retinal thickness of 443 μm in a patient with BCVA 20/600. **(B)** Six weeks after the initial bevacizumab injection there was no change in BCVA, but the central macular thickness increased to 731 μm . On the OCT image it was possible to observe, apart from cystoid macular edema, a fine wrinkling of the inner surface of the retina with associated small bridges of a high reflective preretinal layer, compatible with the development of ERM. **(C)** Seven weeks after a second bevacizumab injection BCVA is 20/600 and central macular thickness reduced to 460 μm . The inner surface of the retina is smoother and there is a continuous preretinal hyper reflective layer. At the inner

vitreous space there are some hyper reflective areas compatible with posterior vitreous cortex. **(D)** Recurrence of macular edema in the presence of fine ERM partially separated from the inner retina. Central macular thickness was 531 μm and BCVA 20/600.

Table 1. Progression of Visual Acuity and Central Macular Thickness During Follow-up.

	Baseline	6 weeks	12 weeks	18 weeks	24 weeks	30 weeks	36 weeks	42 weeks	48 weeks	54 weeks
N	25	25	23	25	12	11	12	6	3	5
BCVA (logMAR)	1.00 ± 0.57	0.83 ± 0.62	0.87 ± 0.69	0.79 ± 0.48	0.62 ± 0.44	0.68 ± 0.69	0.45 ± 0.35	0.50 ± 0.43	0.17 ± 0.23	0.47 ± 0.41
P Value*	---	.005	.023	.139	.071	.012	.005	.285	.180	.042
Central Macular Thickness (µm)	463 ± 204	355 ± 175	375 ± 136	417 ± 173	331 ± 133	298 ± 84	293 ± 95	417 ± 247	224 ± 14	223 ± 20
P Value*	---	.007	.031	.178	.008	.012	.004	.593	.109	.043
Retreatments	---	6	3	7	3	---	---	1	---	---

BCVA: Best corrected visual acuity; * Wilcoxon signed rank test. Values are expressed as mean ± standard deviation.

Table 2. Summary of the cases that developed epiretinal membrane.

	Case 1	Case 2	Case 3	Case 4
Diagnosis	CRVO	CRVO	BRVO	CRVO
Age (years)	47	80	44	38
Time elapsed since diagnosis (months)	38.5	4	6.5	11
Previous treatments	1 IVTA	none	none	1 IVTA
Bevacizumab injections prior to ERM diagnosis	2	1	1	1
Time elapsed since last bevacizumab injection (weeks)	7	6	7	6
Baseline BCVA	20/120	20/600	20/120	20/200
Baseline CMT (μm)	619	443	320	627
Last follow-up BCVA with ERM	20/80	20/600	20/120 +1	20/40
Last follow-up CMT with ERM (μm)	253	531	315	209
Last follow-up after ERM diagnosis (months)	4.8	3	7.5	12

CRVO = central retinal vein occlusion; BRVO = branch retinal vein occlusion; ERM = epiretinal membrane; CMT = central macular thickness; IVTA = intravitreal triamcinolone acetate; BCVA = best corrected visual acuity.





