Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to retinal vein occlusion

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Objective: To evaluate efficacy and safety of intravitreal injections of bevacizumab in the treatment of macular edema secondary to retinal vein occlusion (RVO).

Methods: Prospective study, noncomparative, interventional case series. Twelve consecutive patients (12 eyes) with macular edema associated with nonischemic retinal vein occlusion were treated with intravitreal bevacizumab (1.25 mg). All subjects underwent standardized ophthalmic evaluation at baseline and at weeks 1, 4, 12, and 24, consisting of visual acuity (VA) measurement using ETDRS charts, and imaging with ocular coherence tomography evaluating changes in foveal thickness (FT) and macular volume (MV).

Results: The median age was 66 years (± 4.16), and the median duration of symptoms was 4 months (± 1.81). There were six cases of inferior branch vein occlusion and six cases of superior branch retinal vein occlusion. Mean VA improved from 1.32 ± 0.24 (logMAR values) at baseline to 0.8 ± 0.15 ($p = 0.0003$) at the 6-month follow-up. The macular edema responded promptly, and a trend to restoration of normal macular anatomy was observed at by the seventh day. Mean FT improved from 615.50 ± 116.29 microns to 420 ± 72.53 microns ($p = 0.001$), and the mean MV improved from 19.81 ± 2.31mm3 to 9.23 ± 1.38 ($p = 0.0001$) at the 6-month follow-up.

Keywords: Bevacizumab, retinal vein occlusion, intravitreal injection, vascular endothelial growth factor

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease, after diabetic retinopathy. Visual loss may result from ischemic damage and/or macular edema. Early treatment may be required to improve vision because longstanding macular edema results in irreversible photoreceptor damage (CRVO 1995). Intravitreal triamcinolone is a treatment option that has demonstrated promising short-term results for the management of macular edema associated with RVO (Mohammed et al 2007). A multicenter, randomized and controlled clinical trial (Standard Care Versus Corticosteroid for Retina Vein Occlusion Study) is currently underway.

Retinal vein occlusion is associated with varying amounts of retinal ischaemia and, consequently, increased concentrations of vascular endothelial growth factor (VEGF) (Hayreh 1983). Early case reports on bevacizumab showed an increase in visual acuity (VA) and a decrease in macular edema secondary to exudative age-related macular degeneration (AMD) and central retinal vein occlusion (CRVO) (Rosenfeld et al 2005a). A nonrandomized study of intravitreal bevacizumab in patients with CRVO resulted in reduced macular swelling and increased VA (Iturralde et al 2006). However, because a physiological level of vascular endothelial growth factor may be necessary to maintain the homeostasis of the retina, care might be required to avoid the possible negative consequences of a complete blockade of VEGF.

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These reports, along with results from preclinical and human studies that suggest a possible role of VEGF in RVO and the absence of a proven therapy, prompted us to investigate the effects of intravitreal bevacizumab injection in patients with macular edema associated with RVO.

Methods

Study design

This was a prospective, consecutive, noncomparative study that adhered to the Declaration of Helsinki and which was approved by our institutional review board. An intravitreal off-label bevacizumab injection was recommended. The Spanish Ministry of Health and Consumer Affairs approved compassionate use. Patients were fully informed verbally about the experimental nature of the treatment and they signed an informed consent form.

Cases were recruited from the Hospital Universitari de Bellvitge (Barcelona, Spain) from January–March 2007. Inclusion criteria were: 1) patients aged 50 or older 2) macular edema secondary to nonischemic RVO and 3) VA between 20/400 and 20/50 (Snellen equivalent). Exclusion criteria were: 1) history of retinal surgery or photocoagulation; 2) any history of a thromboembolic event; 3) bleeding disorders; and 4) use of anticoagulative medication other than aspirin. No patient refused treatment.

A comprehensive ophthalmic evaluation was performed; it included a medical history review, best corrected visual acuity testing (using ETDRS charts), slit-lamp biomicroscopy, dilated funduscopic examination using a 78-diopters lens and time domain ocular computed tomography (OCT) (Carl Zeiss Meditec, Dublin, CA, USA) that 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 values for central foveal thickness (FT) and total macular volume (MV) were recorded. Follow-up examinations were scheduled at weeks 1, 4, 12, and 24 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 no loss of follow-up.

Treatment procedure

Patients received an intravitreal dosage of bevacizumab of 1.25 mg (0.05 mL) at baseline and once every four weeks if OCT indicated macular swelling (quantitatively characterized by a macular thickness larger than 250 microns in any of the six radial scans). All treatments were performed in the office using topical anaesthesia (tetracaine+oxibuprocaine) 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 4 days.

Statistical data analysis

All data were collected in an Microsoft Excel 2000 spreadsheet (Microsoft Corporation, Spain). For statistical analysis, the Wllcoxon test was performed. VA measurements were converted to logMAR equivalents to perform analysis. $p < 0.05$ was considered significant.

Results

Twelve patients (seven women and five men) were included. The median age was 66 years and the median duration of symptoms prior to treatment was 4 months. Vein occlusion was located at the inferior branch in six patients and at the superior branch in the remaining six patients. There was a history of hypertension in four patients. All patients completed the 24-week follow-up examination; their baseline characteristics are summarized in Table 1.

Best corrected visual acuity (BCVA) data obtained over the course of the study are summarized in Table 2. Evaluation of BCVA revealed significant improvement at all times compared with baseline. Mean VA improved from 1.32 ± 0.24 (logMAR values) at baseline, to 0.8 ± 0.15 ($p = 0.0003$) at the 6-month follow-up. The macular edema responded promptly, and a reduction in the submacular fluid was observed at the seventh day. At baseline, the mean FT was 615.50 ± 116.29 microns; it declined to 420 ± 72.53 microns ($p = 0.001$). The mean MV improved from 19.81 ± 2.31 mm^3 to 9.23 ± 1.38 mm^3 ($p = 0.0001$) at the 6-month follow-up. Mean changes in parameters recorded by OCT on weeks 1, 4, 12, and 24 post-injection are summarized in Table 3. Overall, four patients were retreated: 2 patients received two consecutive injections of intravitreal bevacizumab, and two patients received three injections. No ocular or systemic adverse events were observed.

Discussion

This study demonstrates the early and clinically relevant benefits of bevacizumab injection for macular edema due to RVO. In this prospective case series, we found that intravitreal

Table 1 Baseline characteristics

Case, age, sex	Affected ye, localization	Duration (months)	logMAR BCVA	OCT FT (microns)	OCT MV (mm^3)
1, 64, F	OD, inferior	2.5	0.63	664	12.91
2, 63, F	OD, inferior	5	1.7	545	22.17
3, 75, M	OD, superior	6	1.05	410	16.65
4, 57, M	OD, superior	3	1.63	667	21.23
5, 67, F	OD, superior	2.5	1.96	601	20.82
6, 66, F	OS, inferior	2	0.62	763	11.9
7, 61 F	OD, superior	3	1.6	495	21.16
8, 75, F	OD, superior	4	1.04	630	15.64
9, 77, M	OS, superior	4	1.62	239	20.22
10, 66, M	OS, inferior	7	1.34	885	12.97
11, 59, M	OS, inferior	6	1.3	498	11.2
12, 79, F	OS, inferior	7	0.96	998	19.81
Median: 66 SD: 7,26 Confidence intervals (CI): 4.16		Median: 4 SD: 1.81 CI: 1.02	Median: 1.32 SD: 0.43 CI: 0.24	Median: 615.50 SD: 205.547 CI: 116.29	Median: 19.81 SD: 4.10 CI: 2.31

Abbreviations: F, female; M, male; SD, standard deviation; OD, right eye; OS, left eye; BCVA, best corrected visual activity; FT, foveal thickness; MV, macular volume.

injections of bevacizumab led both to a significant reduction of FT, as well as to an improvement of visual acuity in patients with RVO. A beneficial effect of intravitreal bevacizumab was observerd as early as the first week and over a 6-month follow-up period.

Our study supports the preliminary results of several recently published papers. The most detailed data on the natural history of CRVO were provided by the Central Vein Occlusion Study Group (CRVO 1995). Clinical outcomes of every new treatment option for CRVO must match with these data. In the natural course of CRVO, only 19% of patients with initial visual acuity of less than 20/200 had a chance of visual acuity of better than 20/200. Patients presenting with initial visual acuity between 20/200 and 20/50 had improvement to better than 20/50 in 19% of cases; in 44% of cases acuity stayed between 20/200 and 20/50. The visual acuity of only 37% of patients became worse than 20/200. Compared with these data, patients treated with intravitreal injections of bevacizumab showed much greater improvement. Priglinger and colleagues (2007) reported improvement in visual acuity from 20/250 at baseline to 20/80 at the 6-month follow-up ($p < 0.001$) in a group of 46 CRVO patients. Mean central retinal thickness decreased from 535 ± 48 microns at baseline to 323 ± 116 microns at the 6-month follow-up (Priglinger et al 2007). In a series of 30 CRVO patients followed for 6 months, Jason and colleagues (2007) reported improvement in VA from 20/394 at baseline to 20/313 at the 3-month follow-up, ($p < 0.05$) and no significant changes after the fourth month. This indicates that bevacizumab represents an effective treatment option for CRVO and that the drug may improve the long-term prognosis of CRVO.

The intravitreal use of bevacizumab may provide anatomical and functional amelioration of the macula in patients with macular edema due to RVO. The electrical responses in the fovea and parafovea of the multifocal electroretinography recording depict a significant improvement at 1 and 3 months after the injection (Moschos and Moschos 2008).

Table 2 logMAR BCVA (baseline and 1, 4 12, and 24 weeks post-injection)

logMAR BCVA baseline	logMAR BCVA, week 1	logMAR BCVA week 4	logMAR BCVA week 12	logMAR BCVA week 24
0.63	0.35	0.17	0.23	0.43
1.7	1.3	0.75	0.77	0.77
1.05	1.01	1.03	1	0.89
1.63	1.47	1.2	1.35	1.17
1.96	0.4	0.43	0.61	0.53
0.62	0.36	0.17	0.23	0.42
1.6	1.2	0.75	0.78	0.76
1.04	1.02	1.02	1	0.86
1.62	1.48	1.3	1.36	1.19
1.34	1	0.78	0.86	0.83
1.3	1.28	1.24	1.28	1.25
0.96	0.5	0.42	0.62	0.56

Note: p (baseline-week 24) = 0.0003
Abbreviation: BCVA, best corrected visual acuity.

Table 3 FT (microns) and MV (mm3) (baseline and 1, 4, 12. and 24 week post-injection)

Case 1	Baseline	Week 1	Week 4	Week 12	Week 24
FT	664	220	166	167	189
MV	12.91	8.48	7.87	8.38	8.34
Case 2					
FT	545	440	165	481	654
MV	22.17	6.96	6.64	9.33	8.35
Case 3					
FT	410	166	496	509	578
MV	16.65	12.17	13.2	13.95	12.95
Case 4					
FT	667	565	459	500	475
MV	21.23	17.32	15.16	15.69	14.63
Case 5					
FT	601	436	175	501	420
MV	20.82	6.66	6.83	9.2	9.5
Case 6					
FT	763	400	170	456	432
MV	11.9	7.47	6.86	7.37	10.56
Case 7					
FT	495	175	195	225	235
MV	21.16	5.95	5.63	8.32	7.35
Case 8					
FT	630	220	460	335	342
MV	15.64	11.16	12.1	12.94	10.55
Case 9					
FT	239	442	336	402	389
MV	20.22	16.31	12.1	14.68	12.48
Case 10					
FT	885	296	450	425	420
MV	12.97	6.25	10.91	10.55	8.95
Case 11					
FT	498	345	450	356	352
MV	11.2	10.72	5.82	10.97	7.55
Case 12					
FT	998	425	182	522	425
MV	19.81	5.55	5.85	8.1	6.98

Notes: p (baseline- week 24): FT = 0.001 MV = 0.0001
Abbreviations: FT, foveal thickness; MV, and macular volume.

Intravitreal injection of triamcinolone acetonide (TA) is another treatment option aimed to reduce macular edema after RVO. Several recent studies report favorable effects of intravitreal injection (4–20 mg) of TA on the course of RVO (Gregory et al 2006). The extent and duration of the effect of intravitreal injection of TA depends on the dose used and the presence of retinal ischemia (Jonas et al 2005). Repeated intravitreal injections of TA are possible; however, after repeated treatments, the effect on reduction of retinal thickness and increase in visual acuity are reduced (Boyd et al 2002; Kupperman et al 2007). Furthermore, although apparently improving the clinical outcome of RVO, repeated intravitreal injections of TA are associated with many potential complications, such as elevated intraocular pressure and cataract formation, which may ultimately decrease the long-term prognosis of RVO (Goff et al 2006). In contrast to intravitreal injection of TA, several injections of bevacizumab appear to have no drug-related complications. However, complications related to repeated intravitreal injections (eg, endophthalmitis, retinal tear, and lens trauma) must be taken into account (Jaissle et al 2006). Fortunately, none of these complications occurred in the present case series; this may be due to the thorough prophylactic, antiseptic regimen applied in our institution to minimize the likelihood of bacterial contamination.

The use of anti-VEGF agents in retinal disease has become increasingly common since the approval (in 2004 and 2006, respectively) of pegaptanib and ranibizumab for age-related maculopathy. These agents are currently being studied for their efficacy against macular edema due to RVO. The anti-VEGF agent most studied in regard to RVO is bevacizumab. Off-label intravitreal injection of bevacizumab was first reported in 2005 to represent a potential therapy for macular edema secondary to CRVO (Rosenfeld et al 2005b). Since then, several additional publications have reported favorable short-term results for reduction of macular edema and improvement of vision in patients with RVO (Spandau et 2006; Pau et al 2007).

Our results suggest a possible short-term benefit for macular architecture and VA; however, it is also clear that such benefits are transient. Continuous VEGF suppression may be required to sustain beneficial effects observed in the short term and the risks associated with multiple intravitreal injections need to be considered. Our data suggest that patients may require several injections to maintain efficacy. Three to four months after the most recent injection, worsening VA was detected in about half of the cases. The data in this study suggest that a single injection of intravitreal bevacizumab has a limited beneficial effect for approximately two months in most patients.

Although VEGF and its receptors represent potential targets for pharmacologic intervention, several important questions remain. Does VEGF play a role in the formation of vascular shunts across ischemic areas? Does continuous blockage of VEGF have a negative effect over the long term? Furthermore, recurrent macular edema may occur in patients

with RVO following treatment with bevacizumab; in some cases, the recurrent macular edema may be more severe than the pre-treatment macular edema (a phenomenon known as "rebound" macular edema) (Matsumoto et al 2007).

The changes observed throughout the present study may provide important clues about drug effects and duration. Favorable macular changes, documented by OCT, were evident as soon as day 7 post-injection. While these improvements were maintained at post-injection week 4, there was a clear tendency for macular edema to recur around week 12; this suggests, therefore, that reinjections might be considered at some point during this period when a 1.25 mg dose regimen is used in setting of ischemic or nonischemic RVO.

The present study does have some limitations that must be recognized: there was no control group; we included only 12 patients and there was only a limited follow-up. However, the promising results reported here indicate that further studies of intravitreal bevacizumab injection for the management of ischemic or nonischemic RVO are justified. Future well-designed studies will help to establish the role of antiangiogenic therapy in the management of RVO.

Disclosure

The authors report no conflicts of interest in this work.

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