

# Intravitreal bevacizumab for the treatment of macular oedema secondary to branch retinal vein occlusion

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## ABSTRACT

**Purpose:** To evaluate the effect of intravitreal bevacizumab (Avastin) injections on visual acuity (VA) and foveal retinal thickness in patients with macular oedema secondary to branch retinal vein occlusion.

**Methods:** A prospective, non-comparative, consecutive, interventional case series of 34 patients. Patients received repeated intravitreal injections of 1.25 mg bevacizumab. Main outcome measures were VA (Snellen charts and ETDRS) and retinal thickness (optical coherence tomography measurements) in a follow-up period of 6 months.

**Results:** Patients presented at a mean age of 69 years (range 44–86). Mean duration of symptoms was 40 weeks (range 1–300). Mean (SD) VA at baseline was 0.79 (0.39) logMAR, improving to 0.51 (0.34) logMAR at 6 months ( $p = 0.009$ ). Mean number of letters on the ETDRS chart at baseline was 45.3 (19.0), improving to 60.6 (19.9) at 6 months ( $p = 0.003$ ). Mean (SD) retinal thickness at baseline was 474 (120)  $\mu\text{m}$ , declining to 316 (41)  $\mu\text{m}$  at 6 months.

**Conclusion:** Intravitreal injection of 1.25 mg bevacizumab appears to be an effective treatment option for branch retinal vein occlusion.

Thus pharmacological inhibition of VEGF appears to be a promising approach for treatment of BRVO, in which the breakdown of the blood/retinal barrier and neovascularisation have important roles.

The VEGF inhibitor bevacizumab (Avastin, rhuMab-VEGF; Genentech, South San Francisco, California, USA) is a full-length humanised monoclonal antibody approved by the Food and Drug Administration, which was originally developed for the treatment of metastatic colorectal cancer. It has recently emerged as a novel therapeutic strategy for retinal diseases, especially age-related macular degeneration, and, in retrospective short-term studies, has also proven to be effective in central retinal and branch retinal vein occlusion.<sup>5–11</sup> None of the clinical and experimental studies published so far have found any drug-related toxic effects on any retinal structures.

This study was conducted to prospectively evaluate the effect of intravitreal administration of 1.25 mg bevacizumab on macular oedema and visual function secondary to BRVO.

## METHODS

### Study design

This study was designed as a prospective, consecutive, non-comparative case series.

Patient eligibility with regard to diagnosis of macular oedema after BRVO was confirmed from optical coherence tomography (OCT) images, fluorescein angiograms and fundus photographs. Patients who had received previous laser treatment within the preceding 6 months were excluded.

All patients gave their written informed consent. They were specifically informed about the off-label character of the treatment and the potential risk of retinal detachment and endophthalmitis, as well as the fact that additional treatment might be required. The study was performed in accordance with the Declaration of Helsinki. Only one eye was selected as the study eye.

In an initial step, patients received an intravitreal injection of 1.25 mg bevacizumab on day 1 and 4 weeks thereafter. After the second injection, the decision on further intravitreal administration of bevacizumab was made on the basis of treatment success, ineffectiveness or toxicity as determined by evaluation of visual acuity and OCT findings. Patients underwent monthly visual acuity testing, ocular pressure measurement, slit lamp and stereoscopic fundus examination, OCT imaging, and fundus photography.

Branch retinal vein occlusion (BRVO) is a common retinal vascular disorder of the elderly.

Associated risk factors include advanced age (usually 60–70 years), arterial hypertension, arteriosclerosis, diabetes mellitus, hyperlipidaemia and smoking.<sup>1</sup> Visual acuity is usually affected only when the area of ischaemia includes the macula or if secondary oedema and/or bleeding involve the macula. The only evidence-based treatment available for macular oedema secondary to BRVO is retinal grid laser photocoagulation based on the results of the Branch Vein Occlusion Study.<sup>2</sup> However, visual outcome for laser-treated patients in this study was a mean gain of 1.33 lines, suggesting the need for advanced therapeutic measurements. In addition, one major drawback of laser photocoagulation is its after-effect of visual field defects, which may increase over time.

Recent studies have shown vascular endothelial growth factor (VEGF) to play a crucial role in the pathogenesis of retinal oedema secondary to vaso-occlusive disease.<sup>3–5</sup> VEGF has been reported to destabilise endothelial tight junctions and promote endothelial cell proliferation secondary to ischaemia, both conditions found in vaso-occlusive retinal disease.<sup>6,7</sup> Upregulation of VEGF is associated with the breakdown of the blood/retina barrier, with the increased vascular permeability resulting in retinal oedema, stimulation of endothelial cell growth, and neovascularisation.<sup>8–10</sup>

## Clinical science

Owing to the off-label character of the intravitreal bevacizumab treatment, a strict treatment protocol was developed to avoid ineffective treatment.

### Treatment success

Treatment success after the second intravitreal bevacizumab injection was determined as follows: (a) best corrected visual acuity score of the study eye of  $\geq 79$  letters (approximate Snellen equivalent of  $\geq 20/30$ ); (b) average retinal thickness in the OCT central subfield of  $\leq 225$   $\mu\text{m}$ . If treatment was discontinued because of success, the patient nevertheless continued to undergo the scheduled monthly assessments. Treatment was restarted if the average macular thickness of the study eye increased by  $\geq 50$   $\mu\text{m}$ , as assessed on OCT scans, or visual acuity decreased by  $\geq 5$  letters and was  $< 74$  letters.

### Treatment ineffectiveness (ie, not even borderline improvement)

If two consecutive monthly bevacizumab injections had not produced at least borderline improvement in the study eye, the treatment was discontinued. Borderline improvement was defined as follows: (a) a decrease in mean retinal thickening of the study eye of at least 50  $\mu\text{m}$ ; (b) an increase in best corrected visual acuity score of at least 5 letters. If the study eye did not show borderline improvement, further treatment with bevacizumab injections was discontinued at the 2-month follow-up.

Patients who discontinued treatment for this reason were also enrolled in the scheduled monthly assessments.

### Outcome measures

The main outcome measures of the treatment were central retinal thickness and visual function. Best corrected visual acuity was tested using Snellen-adjusted charts (Moeller-Wedel M3000, Wedel, Germany) projected at 5 m distance with numeric presentation. Letter numbers were then evaluated using ETDRS charts (Lighthouse International, New York, USA).<sup>12</sup> Additional assessments, consisting of intraocular pressure measurement, slit lamp examination, bilateral stereoscopic fundus biomicroscopy using a 78 diopter lens, retinal thickness measurement using OCT (Stratus OCT-3000; Carl Zeiss Meditec, Dublin, California, USA), and fundus photographs of the posterior pole and the macular area, were performed before treatment and during the follow-up examinations 14 days, 6 weeks and 3, 4 and 6 months after treatment. For statistical analysis, Snellen acuity was converted into the corresponding value in logarithmic minimal angle of resolution (logMAR).

### Injection technique

Topical anaesthesia was achieved before injection using 1% tetracaine eye drops. Before injection, the eye was scrubbed with 10% povidone/iodine. Patients then received a unilateral intravitreal injection of 0.05 ml containing 1.25 mg bevacizu-

mab using a sharp 27-gauge needle at a distance of 3.5–4.0 mm from the limbus.

### Statistical analysis

All data were collected in a MS-Excel 2000 spreadsheet (Microsoft Corporation, Unterschleissheim, Germany) and analysed using SPSS V13.0 for Windows (SPSS Inc, Chicago, Illinois, USA). For statistical analysis, the Wilcoxon test was applied for comparison of multivariables within one group (eg, initial visual acuity versus final visual acuity) and the Mann-Whitney U test was performed for comparison of differences between subgroups. For all statistical tests,  $p < 0.05$  was considered significant.

## RESULTS

Thirty-four patients (21 male) with retinal oedema involving the centre of the macula secondary to BRVO were evaluated. Patients presented at a mean age of 69 years (range 44–86). Mean duration of symptoms from BRVO until study inclusion was 40 weeks (range 1–300). All 34 patients completed the 6-month observation period, attending all control visits.

Fourteen (41%) of the 34 eyes had been pretreated. Two eyes (6%) had received a pars plana vitrectomy with peeling of epiretinal membranes, one with and one without additional sheathotomy. Eleven eyes (32%) had received laser photocoagulation for treatment of macular oedema, three of them combined with intravitreal injection of triamcinolone acetate. One patient (3%) had received an intravitreal injection of triamcinolone acetate alone. The remaining 20 (59%) had not been treated before study inclusion.

The mean number of intravitreal injections performed during the study period was 2.9. Altogether, 15 (44%) eyes received two, 10 (29%) eyes three, six (18%) eyes four, two (6%) eyes five, and one (3%) eye six injections.

Overall mean (SD) visual acuity at baseline was 0.79 (0.39) logMAR (20/120), improving to 0.51 (0.34) logMAR (20/60) at 6 months ( $p < 0.001$ ) (table 1). To be more precise, whereas 29 (85%) of the 34 eyes included in the study initially had visual acuity worse than 20/40 and only five eyes with 20/40 or better (15%), at 6 months, the visual acuity was worse than 20/40 in only 21 cases (62%) and was 20/40 or better in 13 cases (38%). At 6 months, the gain in visual acuity was two or more lines in 21 (62%) and four or more lines in 12 (35%) of the 34 cases.

At baseline, the mean number of letters was 45.3 (19.0) and this improved to 60.6 (19.9) at 6 months ( $p < 0.001$ ). Overall, mean gain between baseline and 6 months was 15.3 (13.5) letters ( $p < 0.001$ ).

Retinal thickness measured by OCT was 474 (120)  $\mu\text{m}$  at baseline and declined to 316 (41)  $\mu\text{m}$  at 6 months ( $p < 0.001$ ).

Subgroup analysis of pretreated cases versus those not pretreated revealed some statistically significant differences. The 14 pretreated eyes showed a mean visual acuity of 0.91 (0.40) logMAR (20/160) at baseline and a mean of 38.0 (17.4) letters, whereas the 20 eyes that had not been pretreated showed a mean baseline visual acuity of 0.71 (0.38) logMAR (20/200) and a mean of 50.4 (18.9) letters ( $p = 0.120$  and  $0.047$ , respectively). At 6 months, eyes that had not been pretreated showed a mean visual acuity of 0.37 (0.27) logMAR (20/50) and a mean of 67.7 (16.5) letters and pretreated eyes achieved a mean visual acuity score of only 0.70 (0.36) logMAR (20/200) and a mean of 50.5 (20.6) letters ( $p = 0.04$  and  $0.012$ , respectively) (figs 1 and 2). In addition, there was a mean letter

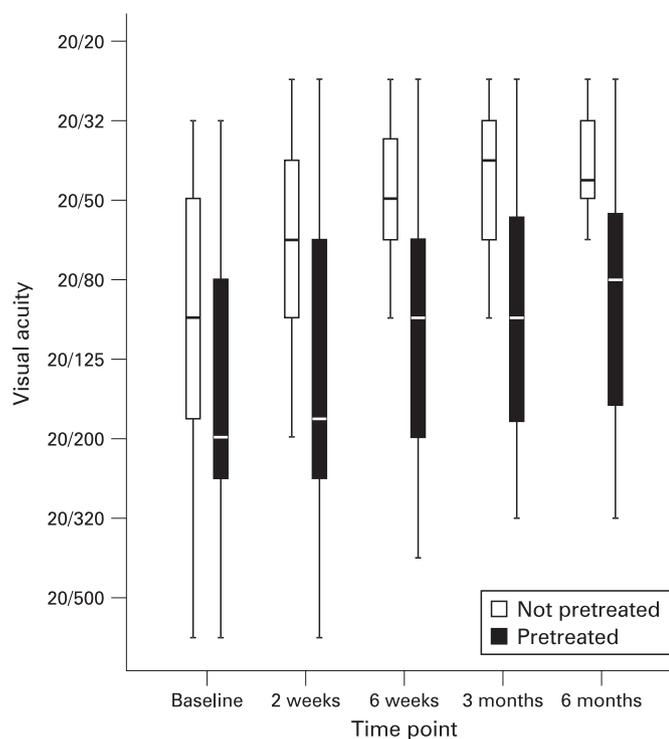
**Table 1** Visual acuity (logMAR, letters on ETDRS chart and OCT) after treatment with bevacizumab

	Baseline	2 weeks	6 weeks	3 months	6 months
logMAR	0.79 (0.39)	0.64 (0.41)*	0.55 (0.35)*	0.49 (0.39)*	0.51 (0.34)*
ETDRS	45.3 (19.0)	51.4 (20.8)*	58.7 (19.8)*	64.1 (21.4)*	60.6 (19.9)*
OCT	474 (120)	368 (82)*	333 (66)*	331 (58)*	316 (41)*

Values are mean (SD).

\* $p < 0.05$  compared with baseline value (Wilcoxon test).

logMAR, logarithm of minimal angle of resolution; OCT, optical coherence tomography.



**Figure 1** Comparison of visual acuity results between pretreated (n = 14) and non-pretreated (n = 20) cases of branch retinal vein occlusion.

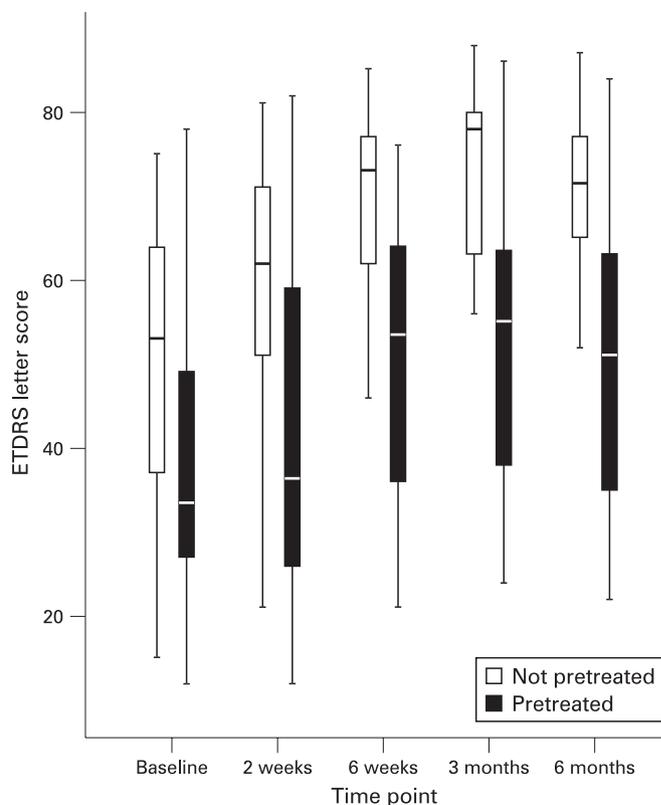
gain of 17.3 (15.3) for eyes that had not been pretreated compared with only 12.5 (11.3) in pretreated eyes ( $p = 0.592$ ).

Although treatment effects in non-pretreated eyes seemed more pronounced, both pretreated and untreated eyes showed significant improvement, as assessed by both logMAR visual acuity ( $p = 0.012$ ,  $p = 0.004$ , respectively) and letter scores ( $p < 0.001$  for both).

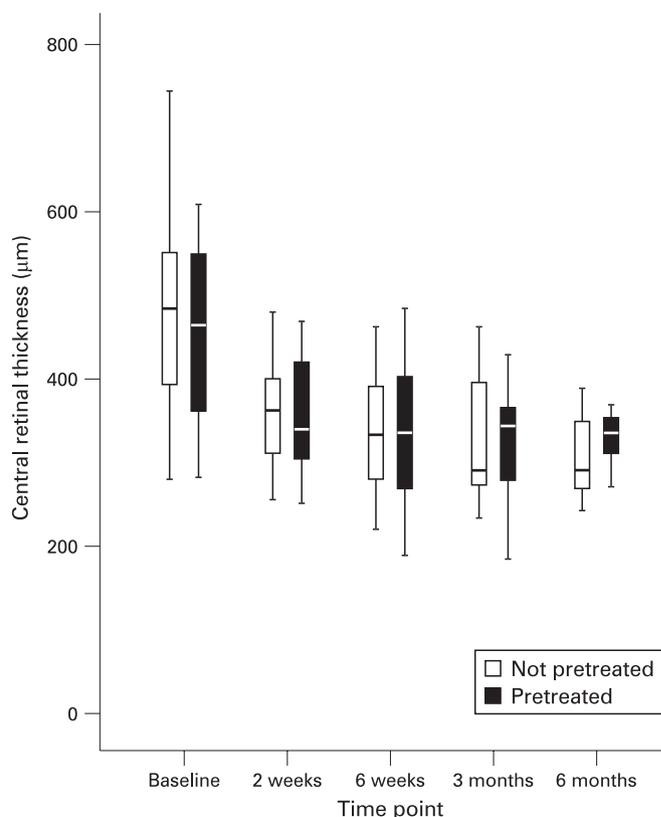
Comparison of retinal thickness measured by OCT between the two groups revealed no significant differences at either baseline or 6 months ( $p = 0.478$  and  $0.071$ , respectively) (fig 3). At baseline, pretreated eyes had a mean central retinal thickness of 492 (179)  $\mu\text{m}$ , decreasing to 332 (28)  $\mu\text{m}$  after 6 months ( $p = 0.004$ ), and the eyes that had not been pretreated had a baseline retinal thickness of 471 (111)  $\mu\text{m}$ , which declined to 304 (46)  $\mu\text{m}$  at 6 months ( $p < 0.001$ ).

Further subgroup analysis was performed to evaluate the effect of the duration of symptoms (decrease in visual acuity secondary to BRVO) before initiation of treatment with intravitreal injections of bevacizumab. In 13 (38%) eyes, treatment was initiated within 90 days of the initial decrease in visual acuity, and 21 (69%) patients were treated more than 90 days after the initial perception of visual decline. Statistical analysis of these two subgroups revealed no significant difference in visual acuity or central retinal thickness (each  $p > 0.366$ ).

In five eyes (15%), minimal recurrent exudation with macula oedema was found at the 5-month visit. In all these cases, the macula was considered to be dry at the 4-month control visit after three intravitreal injections of bevacizumab. At the 5-month visit, these eyes showed new minor exudation with little decrease in visual acuity. After fluorescence angiographic evaluation, additional focal laser photocoagulation was performed. Exudation was successfully eliminated and retinal thickness was stabilised at the 6-month visit.



**Figure 2** Comparison of ETDRS letter scores between pretreated (n = 14) and non-pretreated (n = 20) cases of branch retinal vein occlusion.



**Figure 3** Comparison of central retinal thickness (measured by optical coherence tomography) between pretreated (n = 14) and non-pretreated (n = 20) cases of branch retinal vein occlusion.

No side effects of the intravitreal injection of bevacizumab were seen.

## DISCUSSION

Inhibitory drugs for the VEGF receptor have found their way into ophthalmology for the treatment of various diseases. The first to be introduced was bevacizumab (Avastin), a humanised monoclonal antibody that had previously been used for the treatment of metastatic colorectal cancer. Although it is an off-label drug because of its low toxic side effects, its use in ophthalmology worldwide has shown an unprecedented increase.<sup>15</sup> Previous studies have demonstrated its effectiveness in reducing macular oedema in eyes with retinal vein occlusions and age-related macular degeneration.<sup>5 14–16</sup>

This is the first large prospective clinical trial to demonstrate the effectiveness of intravitreal bevacizumab in reducing macular oedema. The OCT findings show a statistically significant reduction in central retinal thickness at all study time points. Moreover, mean visual acuity scores show significant improvement at all follow-up visits compared with baseline findings: a mean gain of three lines due to a mean increase of 15.3 letters on the ETDRS chart among all the patients.

One drawback of this study is the lack of testing of functional visual acuity, such as reading tests. In patients with focal macular oedema, reading problems are more pronounced than basic recognition of distantly presented optotypes. Evaluation of possible gains in reading performance is planned in a future study.

Subgroup analysis of early versus delayed treatment with intravitreal bevacizumab revealed no significant differences in visual acuity prognosis. This is in contrast with earlier findings of our group on treatment of macular oedema secondary to central retinal vein occlusion with intravitreal bevacizumab.<sup>16</sup> In BRVO, unlike central retinal vein occlusion, perfusion of retinal structures can still be achieved by collaterals to the non-perfused area. This presumably results in less, or delayed, chance of irrevocable damage to the macula, with better prognosis for visual acuity even after delayed treatment of the oedema.

Although there is some controversy about its effectiveness, laser photocoagulation has been proposed to be the best treatment for persistent macular oedema following BRVO.<sup>17 18</sup>

In our study, five patients showed mild recurrent exudation after initially successful bevacizumab treatment. In these patients, complete resorption of macular oedema could be achieved with additional focal laser photocoagulation. Retinal thickness and visual acuity were stable for the whole follow-up period. Two of these cases were pretreated (with pars plana vitrectomy and peeling of the epiretinal membrane) and three were not. From these results, one could conclude that a combined treatment of bevacizumab and focal laser photocoagulation might be an even more effective approach. However, considering the non-pretreated cases, only two (10%) of 20 patients in our trial needed additional laser treatment. Further studies will be necessary to determine whether this combined treatment would reduce the number of bevacizumab injections needed to resolve persistent oedema or if bevacizumab treatment can effectively reduce the necessity for grid laser photocoagulation in the long term.

Subgroup analysis revealed that pretreatment of BRVOs before bevacizumab injections resulted in a worse prognosis than when bevacizumab was the initial treatment. Barbazetto

and Schmidt-Erfurth<sup>19</sup> have shown that grid laser photocoagulation causes an increase in central scotoma size in patients with macular oedema after BRVO. Laser treatment led to decreased mean visual acuity scores in these eyes after 3 months. Analogously to that study, most pretreated eyes in our study had laser photocoagulation, which may explain the reduced visual acuity in this subgroup. In addition, the duration of symptoms was significantly longer in the pretreated cases than the non-pretreated cases: 53.7 (49) vs 28.7 (68) weeks ( $p=0.001$ ). The longer duration of macular oedema may also have contributed to the worse results for visual acuity. Although this may be true, even these eyes benefited from the intravitreal bevacizumab injections, on average, gaining 12.5 letters on the ETDRS chart.

In the Branch Vein Occlusion Study, eyes with macular oedema after BRVO either received grid laser photocoagulation or remained untreated. Eyes either received grid laser photocoagulation or remained untreated. After 3 years, 63% of eyes in the laser-treated group had gained two or more lines, whereas only 36% of untreated eyes reached that level.<sup>2</sup> Bevacizumab treatment of BRVOs in the present study produced a similar outcome to the Branch Vein Occlusion Study: 62% of patients gained two or more lines compared with prior treatment. However, an increase in visual acuity after bevacizumab treatment is observed after only a very short observation period and the effect of bevacizumab lasted for 6 months. Further studies are necessary to evaluate the long-term effect of anti-VEGF therapy for the treatment of macular oedema secondary to BRVO.

In summary, we have shown that intravitreal injections of bevacizumab are an effective treatment option for eyes with macular oedema due to BRVO. Whether additional laser photocoagulation would produce additional benefit needs to be further evaluated. We can recommend this treatment as a primary approach for eyes with macular oedema secondary to BRVO.

**Competing interests:** None declared.

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