Clinical, Anatomic, and Electrophysiologic Evaluation Following Intravitreal Bevacizumab for Macular Edema in Retinal Vein Occlusion

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• PURPOSE: **To investigate clinical, anatomic, and electrophysiologic response after single intravitreal injection of bevacizumab for macular edema attributable to retinal vein occlusion.**

• DESIGN: **Prospective nonrandomized, interventional case series.**

• METHODS: **Twenty-one patients with macular edema attributable to vein occlusion received intravitreal injection of bevacizumab 1.25 mg. Nine patients had central retinal vein occlusion (CRVO), and 12 patients had branch retinal vein occlusion (BRVO). Complete ophthalmic examination including optical coherence tomography (OCT) was done at baseline and follow-up visits. Fifteen patients underwent fluorescein angiography at baseline. Selected patients underwent electroretinography (ERG) and visual evoked potential (VEP) at baseline and follow-up. Follow-up was for 12 weeks.**

• RESULTS: **At baseline, mean visual acuity was 20/381 (median, 20/400) and showed improvement to mean 20/135 (median, 20/60) after one month, ($P = .001$). At 12 weeks, mean visual acuity was 20/178 (median, 20/80) ($P = .001$). The mean central retinal thickness (CRT) was 647.81 μm (median, 609.00 μm) at baseline and decreased to mean 293.43 μm (median, 222.00 μm) at one month ($P = .001$). At 12 weeks, mean CRT was 320.90 μm (median, 280.00 μm) ($P = .001$). ERG and VEP showed no worsening of the waveforms. There was no significant difference in the visual outcome between the BRVO and CRVO groups.**

• CONCLUSION: **Intravitreal injection of bevacizumab appears to result in significant short-term improvement of visual acuity and macular edema secondary to vein occlusion. The present report confirms the previous studies. No ocular toxicity or adverse effects were observed. However, prospective, randomized, controlled long-term studies are required with an adequate number of patients. (Am J Ophthalmol 2007;143:601–606.**

Accepted for publication Dec 17, 2006.

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RETINAL VENOUS OCCLUSIVE DISEASE IS PROBABLY the most common retinal vascular disorder after diabetic retinopathy. Macular dysfunction occurs in almost all eyes with central retinal vein occlusion (CRVO). Decrease in central vision occurs due to persistent macular edema, nonperfusion of the parafoveal capillaries, and damage to the retinal pigment epithelium attributable to extensive macular hemorrhage.[1] There is no proven therapy for macular edema associated with CRVO. The vision-limiting complications in branch retinal vein occlusions (BRVO) are macular edema, macular nonperfusion, and vitreous hemorrhage from neovascularization.

The retinal vein occlusion causes increased intraocular vascular endothelial growth factor (VEGF) that varies with the disease severity.[2] VEGF is a vascular permeability factor. It induces vascular fenestration as well as an increase in permeability of microvessels leading to deposition of proteins in the interstitium that facilitates the process of angiogenesis.[3] Increased levels of VEGF also leads to macular edema.[4] VEGF is also implicated as the major angiogenic stimulus responsible for neovascularization in age-related macular degeneration (AMD)[5] and diabetic retinopathy.[6] One possible strategy for treating retinal neovascularization, choroidal neovascularization, and macular edema is to inhibit VEGF activity by competitively binding VEGF with a specific neutralizing anti-VEGF antibody.

Bevacizumab (Avastin, Genentech, Inc, San Francisco, California, USA) is a full-length humanized monoclonal antibody against VEGF. It binds and inhibits all the biologically active forms of VEGF.[7] Michels and associates showed that intravenous bevacizumab administered in two or three infusions at a dose of 5 mg/kg every two weeks decreased the central retinal thickness and improved vision.[8] In a short-term study, intravitreal bevacizumab for AMD resulted in the improvement of multifocal ERG (mfERG) macular function responses and relatively safe Ganzfeld-ERG (G-ERG) responses.[9] In this study, we evaluated the clinical, anatomic and electrophysiologic response after a single intravitreal injection of 1.25 mg of bevacizumab for macular edema secondary to retinal vein occlusion.

0002-9394/07/$32.00
doi:10.1016/j.ajo.2006.12.037

METHODS

WE CONDUCTED A NONRANDOMIZED, PROSPECTIVE STUDY after approval of the Institutional Ethical Committee, and all patients signed an informed consent to participate in the study. This study has been registered with www.clinicaltrials.gov, and the registration information is available to the public through the Web site http://www.clinicaltrials.gov/, registration number NCT00403026. Twenty-one eyes of 21 consecutive patients with macular edema attributable to vein occlusion with vision less than 20/80 underwent intravitreal injection of bevacizumab. Patients with uncontrolled systemic diseases were excluded from the study.

All patients underwent best-corrected visual acuity (BCVA) measurement with Snellen chart, intraocular pressure (IOP) measurement using noncontact method, ophthalmic examination including slit-lamp biomicroscopy, and central retinal thickness (CRT) measurement by fast macular scans using optical coherence tomography (StratusOCT, Carl Zeiss Meditec, Dublin, California, USA) at baseline and follow-up visits on the second day, first week, fourth week, eight weeks, and 12 weeks after treatment. The map was created from six consecutive diagonal 6-mm scans that intersected at the fovea. The fundus image generated by the OCT machine during the procedure was used to center the scan at the fovea for each examination.

Fifteen out of 21 patients underwent fundus fluorescein angiography at baseline. None of these patients had retinal neovascularization or rubeosis. Eight patients underwent baseline multifocal electroretinogram (mfERG) and Full-field electroretinography (full-field ERG) using International Society for Clinical Electrophysiology of Vision (ISCEV) compliant protocol[10,11] on Metrovision ERG system (Pe'rerchies, France). Six major variables were studied including dark-adapted b-wave amplitude and implicit time, light-adapted b-wave amplitude and implicit time, light-adapted flicker implicit time, and amplitude. The mfERG responses were measured using a custom five-minute m-sequence–derived protocol (Metrovision). The stimulus matrix consisted of 61 hexagonal elements displayed on cathode ray tube monitor. N_1P_1 amplitude and implicit time (nV/deg^2) was studied in the central 15 degree. Repeat tests were done at one week, four weeks, and 12 weeks after intravitreal injection of bevacizumab. Pattern visual evoked potential (VEP) was done on two patients at baseline and four weeks after treatment, using an ISCEV–compliant protocol on the Metrovision system.[12] Intravitreal injection of bevacizumab 1.25 mg/0.05 ml was given under all aseptic precautions, and prophylactic topical antibiotics were given for one-week postinjection.

Snellen visual acuity was converted to logMAR units before analysis. All continuous variables were expressed as mean ± standard deviation. Normality of the data was assessed by the usual diagnostics: normal probability plots and the Shapiro-Wilk test. To determine if significant changes occurred from baseline to the final outcome, the Wilcoxon –signed-rank test was used. A P value $<.05$ was considered statistically significant. The data were analyzed using Statistical Software (SPSS, version 10.5, SPSS Inc, Chicago, Illinois, USA).

RESULTS

A TOTAL OF 21 EYES OF 21 PATIENTS WERE ANALYZED. Eleven patients (52.4%) were male, and 10 were (47.6%) female. The mean age was 66.7 ± 8.5 years (range, 42 to 78 years). Nine patients had central CRVO, and 12 patients had BRVO. Fourteen patients were hypertensive, three were diabetic, two patients were both diabetic and hypertensive, and in two patients, no cause was found. All patients had cystoid macular edema (CME) on OCT imaging with BCVA of 20/80 or less. None of the patients had undergone any modalities of treatment for vein occlusion. OCT imaging of three patients (Cases 1, 10, and 11) with the corresponding color fundus photographs are shown in Figure 1. Follow-up was for 12 weeks. Mean BCVA was 20/381 (logMAR, 1.28 ± 0.55), median 20/400 (logMAR 1.3). Mean CRT was 647.81 ± 303.22 μm (median, 607.0) at baseline. The mean baseline BCVA in the CRVO group was 20/468 (logMAR, 1.37 ± 0.54), median 20/400 (logMAR, 1.3). In the BRVO group, the mean BCVA was 20/333 (logMAR, 1.22 ± 0.58), median 20/225 (logMAR 1.05). Baseline CRT in the CRVO group was mean 614.6 ± 184.86 μm, median 611.0 μm. In the BRVO group, the mean CRT was 672.8 ± 375.14 μm, and the median was 575.5 μm. The mean IOP was 16 mm Hg. Eight patients underwent full-field ERG and mfERG. Two patients underwent pattern VEP. The visual acuity and CRT data at baseline, at four weeks, and 12 weeks after intravitreal injection of bevacizumab in the CRVO and the BRVO groups are presented in Tables 1 and 2, respectively.

At four weeks after intravitreal injection of bevacizumab for macular edema in vein occlusion, 16 of 21 patients (76.2%) showed improvement of vision. Mean BCVA was 20/135 (logMAR, 0.82 ± 0.59), and the median was 20/60 (logMAR, 0.48), a difference from baseline that was statistically significant (P = .001). The percentage improvement in BCVA from baseline was 34.4. CRT decreased to mean 293.43 ± 130.40 μm (median, 222.00 μm) compared to baseline. The difference from baseline was statistically significant (P = .001). The percentage decrease in CRT from baseline was 54.7. OCT images of three patients (Cases 1, 10, and 11) is shown in Figure 1. Five patients (23.8%) maintained baseline vision, although there was significant decrease in mean CRT to 349.60 ± 251.14 μm from baseline mean CRT 647 + 303.22 μm. In the CRVO group, the mean BCVA was 20/227 (logMAR, 1.05 ± 0.63), median 20/200 (logMAR,

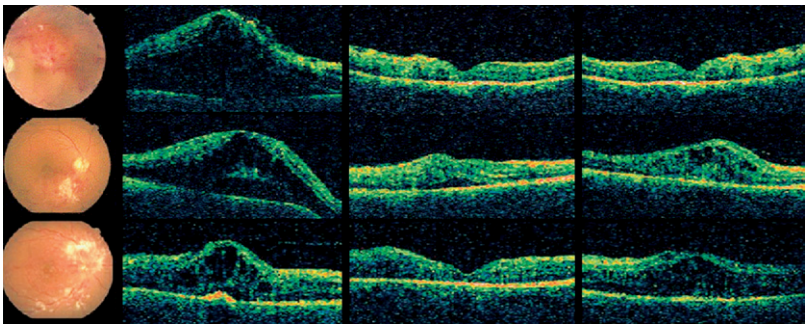

FIGURE 1. Color fundus photographs of Case 1 (Top row), Case 10 (Middle row), and Case 11 (Bottom row) at baseline and successive optical coherence tomography (OCT) scans at baseline, four weeks, and 12 weeks after intravitreal injection of 1.25 mg bevacizumab for macular edema in vein occlusion. (Top row) Left to right of Case 1: (1) Color fundus photograph shows superotemporal branch retinal vein occlusion (BRVO) with dense intraretinal hemorrhage and macular edema. (2) OCT scan at baseline showing massive cystoid macular edema (CME) and visual acuity was 20/2000. (3) OCT scan at four weeks after intravitreal injection of bevacizumab shows reduction of macular edema and visual acuity improved to 20/60. (4) OCT scan at 12 weeks after intravitreal injection of bevacizumab shows recurrence of macular edema with a drop in visual acuity to 20/80. (Middle row) Left to right of Case 10: (1) Color fundus photograph showing inferotemporal BRVO, cotton wool spots, and intraretinal hemorrhage with macular edema. (2) OCT scan shows CME and visual acuity was 20/250. (3) OCT scan at four weeks after intravitreal injection of bevacizumab shows reduction of macular edema and improvement of visual acuity to 20/30. (4) OCT scan at 12 weeks after intravitreal injection of bevacizumab shows recurrence of macular edema with a drop in vision to 20/60. (Bottom row) Left to right of Case 11:(1) Color fundus photograph shows central retinal vein occlusion (CRVO) with optic nerve swelling, cotton wool spots and intraretinal hemorrhage obscuring the fovea. (2) OCT scan shows CME, and the visual acuity was 20/400. (3) OCT scan at four weeks after intravitreal injection of bevacizumab shows reduction in macular edema, but visual acuity remained 20/400. (4) OCTscan at 12 weeks after intravitreal injection of bevacizumab shows recurrence of macular edema, and the visual acuity remained at 20/400. (There was no improvement of vision, although there was considerable decrease in central retinal thickness attributable to the dense intraretinal hemorrhage involving the fovea.)

TABLE 1. Change in BCVA and CRT on Optical Coherence Tomography Imaging Following Intravitreal Injection of Bevacizumab (Avastin) in the CRVO Group

			Change in BCVA After Intravitreal Injection of Bevacizumab			Change in CRT After Intravitreal Injection of Bevacizumab	
Serial No.	Age (Years)	Baseline BCVA (Snellen)	BCVA at 4 Weeks (Snellen)	BCVA at 12 Weeks (Snellen)	Baseline CRT (μm)	CRT at 4 weeks (μm)	CRT at 12 weeks (μm)
1	48	20/400	20/120	20/200	708	222	230
2	65	20/400	20/200	20/100	611	204	240
3	60	20/4000	20/400	20/800	541	177	200
4	68	20/100	20/40	20/60	640	268	320
5	42	20/400	20/400	20/400	1022	378	340
6	65	20/200	20/60	20/80	411	212	240
7	68	20/2000	20/2000	20/2000	400	200	220
8	70	20/2000	20/2000	20/2000	647	200	230
9	54	20/100	20/40	20/60	551	200	250

BCVA= best-corrected visual acuity; CRT = central retinal thickness; CRVO = central retinal vein occlusion.

1). In the BRVO group, the mean BCVA was 20/91 (logMAR, 0.66 ± 0.51), median 20/60 (logMAR, 0.48). The difference in BCVA compared to baseline in the CRVO and BRVO groups was not statistically significant ($P = .169$). CRT in the CRVO group, the mean was 229 ± 61.15 μm (median, 204 μm). In the BRVO group, the mean was 341.8 ± 149.17 μm (median, 319 μm). The difference in CRT compared to baseline in the CRVO and BRVO groups was statistically significant ($P = .028$). The percentage decrease in CRT in the CRVO and BRVO groups was 62.7 and 49.2, respectively. The mean IOP was 16 mm Hg. The full-field ERG and mfERG responses of the eight patients showed no significant worsening. Most of the values were within the limits of normal variation. The full-field summed ERG waveform of Case 2 before treatment and after four weeks of treatment is presented in Figure 2. The central 15 degrees mfERG trace arrays data of Case 2 is illustrated in Figure 3. The mfERG waveform

TABLE 2. Change in BCVA and CRT on Optical Coherence Tomography Imaging Following Intravitreal Injection of Bevacizumab (Avastin) in the BRVO Group

Serial No.	Age (Years)	Baseline BCVA (Snellen)	Change in BCVA After Intravitreal Injection of Bevacizumab: BCVA at 4 Weeks (Snellen)	Change in BCVA After Intravitreal Injection of Bevacizumab: BCVA at 12 Weeks (Snellen)	Baseline CRT (μm)	Change in CRT After Intravitreal Injection of Bevacizumab: CRT at 4 Weeks (μm)	Change in CRT After Intravitreal Injection of Bevacizumab: CRT at 12 Weeks (μm)
1	78	20/4000	20/60	20/80	1600	232	270
2	48	20/100	20/30	20/60	1200	428	522
3	57	20/2000	20/2000	20/2000	669	212	337
4	57	20/160	20/80	20/100	401	359	400
5	62	20/2000	20/400	20/400	800	600	660
6	60	20/100	20/60	20/80	544	279	400
7	61	20/100	20/40	20/60	401	359	400
8	68	20/100	20/60	20/80	325	177	400
9	58	20/800	20/50	20/80	508	217	250
10	70	20/100	20/40	20/60	607	220	300
11	55	20/100	20/40	20/60	400	400	280
12	60	20/400	20/400	20/400	618	618	250

BCVA = best-corrected visual acuity; CRT = central retinal thickness; BRVO = branch retinal vein occlusion.

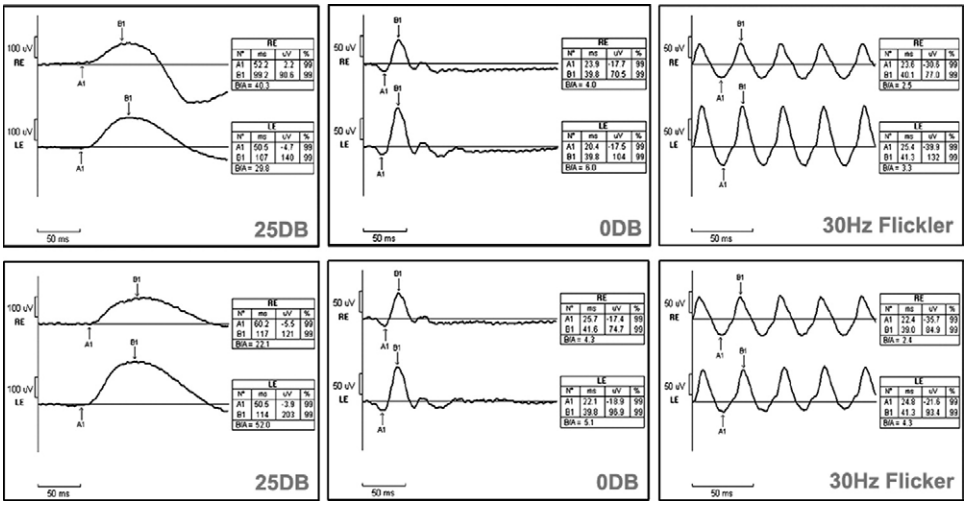

FIGURE 2. Full-field electroretinogram waveforms of Case 2, before and after intravitreal injection of 1.25 mg bevacizumab for macular edema in vein occlusion. (Top row) Full-field electroretinogram tracing of Case 2 before intravitreal injection of bevacizumab for macular edema in vein occlusion. (Bottom row) Full-field electroretinogram tracings of the same patient show no worsening of the waveforms after four weeks of treatment.

showed no worsening after treatment, and, in fact, showed improved central waveforms after treatment in some patients. Pattern VEP responses done in two patients did not show any toxic effect on the optic nerve conduction. No serious ocular or systemic side effects were noted in any of the patients.

At 12 weeks after intravitreal injection of bevacizumab for macular edema in vein occlusion, there was slow deterioration of vision in all the patients (not below the baseline) with recurrence of macular edema. Mean BCVA 20/178 (logMAR, 0.94 ± 0.54), median 20/80 (logMAR, 0.6). The difference in the BCVA compared to baseline was statistically significant ($P = .001$). The percentage improvement BCVA from baseline was 26.60. CRT mean was 320.90 ± 112.98 μm (median, 280 μm). Compared to baseline, the difference was statistically significant ($P = .001$). The percentage decrease in CRT from baseline was 50.50. Figure 1 shows the increase in CRT of Cases 1, 10, and 11 at 12 weeks. Five patients (23.8%) maintained baseline vision, although there was significant decrease in mean CRT to 395.80 ± 182.87 μm compared to baseline. In the patients who had improvement of vision, the mean CRT was 305.38 ± 332.90 μm compared to the baseline. Between these two groups, the change in CRT was not

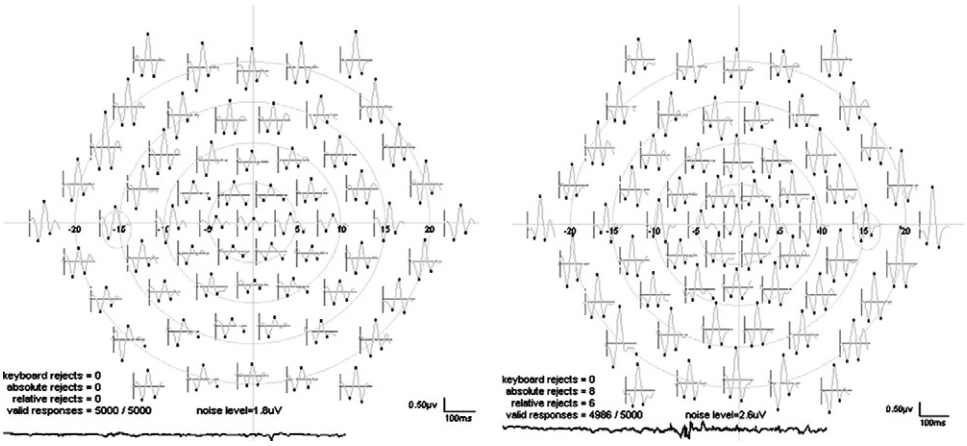

FIGURE 3. Multifocal electroretinogram (mfERG) data of central 15 degrees trace arrays of Case 2, before and after intravitreal injection of 1.25 mg bevacizumab for macular edema in vein occlusion. (Left) mfERG trace arrays of left eye (OS) before intravitreal injection of bevacizumab for macular edema in vein occlusion. (Right) mfERG trace arrays of the same patient showing no worsening of the waveform after treatment.

statistically significant ($P = .573$). In the CRVO group, the mean BCVA was 20/278 (logMAR, 1.14 ± 0.61), median 20/200 (logMAR, 1). In the BRVO group, the mean BCVA was 20/126 (logMAR, 0.8 ± 0.45), median 20/80 (logMAR, 0.6). The difference in visual outcome compared to baseline in the CRVO and the BRVO group was not statistically significant ($P = .193$). Mean CRT in the CRVO group was 252.2 ± 46.58 μm, median 240 μm. In the BRVO group, mean CRT was 372.4 ± 121.96 μm, median 368.5 μm. The difference in CRT compared to the baseline in the CRVO and BRVO groups was statistically significant ($P = .003$). The percentage change in CRT from baseline in CRVO and BRVO was 59.0 and 44.60, respectively. The mean IOP remained at 16 mm Hg. Full-field ERG and mfERG responses in all eight patients tested at 12 weeks showed no significant change. The pattern VEP also did not show changes in waveforms. There were no serious ocular or systemic adverse effects.

DISCUSSION

USE OF BEVACIZUMAB IN THE TREATMENT OF VARIOUS retinal disorders is increasingly being reported.[8,14–17]

Central retinal vein occlusions are associated with varying amounts of retinal ischemia and consequently increased concentrations of VEGF.[13] Rosenfeld and associates were the first to report the efficacy and OCT changes following intravitreal injection of bevacizumab for recurrent macular edema secondary to CRVO in an eye previously treated by intravitreal triamcinolone acetonide injection.[14] In a short-term study, Iturralde and associates treated 16 eyes of CRVO with macular edema, which had failed intravitreal corticosteroid therapy, and nearly every eye showed some anatomic or visual acuity improvement.[15] Spandau and associates also found beneficial effects of intravitreal injection of bevacizumab in a nonischemic CRVO with macular edema.[16]

Our present study confirms the previous reports on intravitreal injection of bevacizumab for macular edema in vein occlusion. We report a series of patients who received a single intravitreal injection of bevacizumab 1.25 mg in 0.05 ml for central and BRVO with macular edema and analyzed the clinical and anatomic outcomes. To provide additional insight into the safety of intravitreal bevacizumab, we performed electrophysiologic tests to study retinal toxicity.

Our nonrandomized, uncontrolled, prospective, interventional study showed marked short-term improvement of vision and reduction of macular edema following intravitreal injection of bevacizumab in most of the patients. However, in 23.8% of the patients, there was reduction in macular edema with no improvement of vision attributable to foveal hemorrhage in three patients and ischemic maculopathy in two patients. Maximum improvement of visual acuity and decrease in CRT was seen by the second week, which was maintained approximately until eight weeks in most of the patients. The duration of action of intravitreal bevacizumab is currently unknown.[17] Reinjections may be necessary to maintain a lasting beneficial effect.

Previous study by Iturralde and associates reported a significant decrease in macular edema with improvement of vision in patients with central retinal vein occlusions following intravitreal injection of bevacizumab 1.25 mg in 0.05 ml.[15] The patients received a mean of 2.8 injections of bevacizumab per eye, unlike our study, in which we have included even branch retinal vein occlusions with macular edema, and we have analyzed the outcomes after a single injection of bevacizumab 1.25 mg in 0.05 ml.

We did not find any statistically significant difference in visual outcome in branch retinal vein occlusion and central retinal vein occlusion groups at either four weeks or 12 weeks. However, there was a statistically significant

difference in CRT between the CRVO and BRVO groups at four weeks and 12 weeks. Testing for retinal function by full-field ERG, mfERG, and pattern VEP studies showed no short-term safety concerns of intravitreal bevacizumab. Therefore, the off-label use of bevacizumab therapy probably has no adverse effects or ocular toxicity. We also did not find direct correlation of visual acuity and CRT with electrophysiologic responses in this small number of patients studied. No systemic side effects were observed. No ocular side effects such as cataract, increased IOP, retinal tear, retinal detachment, intraocular inflammation, or endophthalmitis were encountered in any of the patients. We included all patients who had vein occlusion with macular edema regardless of the ischemic status or duration of the symptoms. Almost all the patients had recurrence of macular edema with a decrease in visual acuity by eight to 12 weeks. It is most likely that the eyes receiving early treatment might benefit more than the eyes receiving delayed treatment.

The release of VEGF in vein occlusions is thought to be stimulated by ischemia, and the degree of ischemia may vary in each eye in different subgroups of vein occlusions. Therefore, we believe that the treatment (dose and frequency of intravitreal bevacizumab) should also be individualized in each case.

Because single intravitreal injections led to recurrence of macular edema, and a decrease in visual acuity repeat injections might be necessary after six weeks, as the drug is well tolerated and has no safety concerns in this short-term study. A dose-escalation strategy to establish a dose-response curve as suggested in previous study should also be included.[14] Although the short-term results are promising, randomized controlled, long-term studies in an adequate number of patients in all subgroups of vein occlusions should be considered. The factors such as ischemic status of the eye, severity of macular edema, pre- and posttreatment levels of VEGF in ocular fluids might be helpful in further studies.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR financial conflict of interest. Involved in conception and design of study (S.A.P., R.S., P.B.V.); analysis and interpretation (S.A.P., R.S., P.B.V., V.G., N.K.Y., R.B.B.); writing the article (S.A.P.); critical revision of the article (S.A.P., P.B.V., R.B.B., K.M.N.); final approval of article (S.A.P., P.B.V., V.G., N.K.Y., R.S., K.B.S., R.B.B., K.M.N.); data collection (S.A.P., R.S., P.B.V., V.G., N.K.Y.); provision of materials and patients (K.B.S.); statistical expertise (S.A.P., P.B.V., R.B.B.); literature search (R.B.B.); and administrative and technical logistic support (K.M.N., K.B.S.).

The authors would like to thank Jagannatha P. Suryanarayana, MSc, Statistics Manager, GlaxoSmithKline Pharmaceuticals Limited, Bangalore, India, for his statistical assistance.

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Biosketch

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Biosketch

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