

Shunt Vessels and Outcomes in Patients With CRVO Treated With Bevacizumab

The results of a study to investigate the impact of bevacizumab on shunt vessel development and evaluate anatomical outcomes.

**BY AMAN SHUKAIRY, MD; CHIRAG PATEL, MD; CHRISTOPHER SINGH, MD;
JAMES PUKLIN, MD; AND TAMER H. MAHMOUD, MD, PhD**

Central retinal vein occlusion (CRVO) is second only to diabetic retinopathy as a vascular cause of vision loss.¹ Visual morbidity and blindness are most commonly due to macular capillary nonperfusion and persistent macular edema, as well as macular hemorrhage, vitreous hemorrhage, retinal detachment, and neovascular glaucoma.^{1,2} As the precipitating event in CRVO is thought to be intravascular venous thrombosis,^{3,4} restoration of venous flow occurs by recanalization of the central retinal vein,³ or by the development of collateral vessels.^{3,4}

Optociliary shunt vessels are known to develop in CRVO,⁵ and studies have shown that they significantly drain the retinal venous circulation into the choroidal vasculature, then into the vortex veins.⁵⁻⁷ Collateral veins have also been shown to be negatively associated with anterior segment neovascularization after CRVO⁷ and with better visual acuity outcomes and accelerated resolution of retinal edema in CRVO eyes treated with radial optic neurotomy.⁸

Concentrations of vascular endothelial growth factor (VEGF) are elevated in the aqueous fluid of eyes with CRVO, with highest concentrations in the presence of iris neovascularization.^{1,9-11} VEGF promotes angiogenesis by increasing endothelial cell migration and proliferation, and it increases vascular permeability through breakdown of the blood retinal barrier.¹²⁻¹⁴ Prospective studies using anti-VEGF therapy in the form of bevacizumab

(Avastin, Genentech, Inc.) have shown significant improvements in visual acuity and mean central retinal thickness in patients with CRVO.^{1,2} However, as VEGF is required for vasculogenesis, its presence may be necessary for the formation of optociliary shunt vessels, in which case VEGF inhibition would actually prove to be detrimental.²

We performed a study to investigate the impact of intravitreal bevacizumab on the development of optociliary shunt vessels in patients with macular edema secondary to CRVO and to evaluate the functional and anatomical outcomes in patients who developed shunt vessels vs patients who did not.

METHODS

A retrospective interventional study of patients diagnosed with CRVO treated with intravitreal bevacizumab for macular edema was performed. Eyes with fundus photography and central subfield foveal thickness (CFT) measurements by optical coherence tomography (OCT) at two or more occasions were included. Fundus photographs at initial and all subsequent visits were examined to assess the appearance of collateral shunt vessels. Fluorescein angiograms were reviewed to evaluate the perfusion status of the involved eye.

Visual acuity and CFT values at onset and last follow-up visit were recorded. Diagnosis of ischemic CRVO was based on the identification of greater than 10 disc areas

of capillary nonperfusion on fluorescein angiogram.^{15,16} Patients were divided into two groups based on whether they developed shunt vessels. Patients were then further subdivided into ischemic and nonischemic CRVO subsets within each group. Statistical analysis was performed using paired t-tests. A probability value of less than 0.05 was considered significant.

RESULTS

Seventeen patients with CRVO injected with intravitreal bevacizumab for macular edema met inclusion criteria. The average age of patients was 65.6 years. Eight eyes (47.1%) were diagnosed as ischemic CRVO and nine (52.9%) as nonischemic. Nine patients (52.9%) developed shunt vessels (group 1), and eight patients (47.1%) did not (group 2).

In group 1, five patients (55.6%) developed shunt vessels prior to intravitreal bevacizumab injection, and four patients (44.4%) developed shunt vessels after injection. Patients were injected an average of 3.8 times. The mean time to development of optociliary shunt vessels after the diagnosis of CRVO was 40.4 days. The mean follow-up time for group 1 was 14 months (range, 3–34 months).

The mean initial best corrected visual acuity (BCVA) of all group 1 patients was 20/400 (logMAR 1.3), which significantly improved to a mean final BCVA of 20/125 (logMAR 0.8, $P=.008$). Mean CFT for all group 1 patients decreased from 567.4 μm (initial) to 347.1 μm (final), an improvement that was statistically significant ($P=.008$). Six eyes (66.6%) in group 1 were classified as nonischemic CRVO, and three eyes (37.4%) as ischemic CRVO. In the nonischemic CRVO eyes in group 1, mean initial BCVA was 20/200 (logMAR 1.1), improving to a mean final BCVA of 20/100 (logMAR 0.7, $P=.07$), and mean initial CFT decreased from 564.7 μm to 252.2 μm (final), an improvement that was statistically significant ($P=.01$). In the ischemic CRVO eyes in group 1, mean initial BCVA was 20/600 (logMAR 1.5), improving to a mean final BCVA of 20/200 (logMAR 1.0, $P=.10$), and mean initial CFT decreased from 573.0 μm to 421.3 μm (final, $P=.40$).

In group 2, patients were injected an average of 4.3 times, and mean follow-up time was 26 months (range, 13–46 months). The mean initial BCVA of all group 2 patients was 20/250 (logMAR 1.1), only mildly improving to a mean final BCVA of 20/200 (logMAR 1.0, $P=.23$). Mean CFT for all group 2 patients remained stable from 316.4 μm (initial) to 327.5 μm (final, $P=.89$). Three eyes (33.3%) in group 2 were classified as nonischemic CRVO, and five eyes (62.5%) as ischemic CRVO. In the nonischemic CRVO eyes in group 2, mean initial BCVA was 20/100 (logMAR 0.7) and mean final BCVA was 20/63

(logMAR 0.5, $P=.42$). Mean initial CFT for the nonischemic CRVO eyes in group 2 increased from 312.7 μm to 353.3 μm (final, $P=.09$). In the ischemic CRVO eyes within group 2, mean initial BCVA was 20/500 (logMAR 1.4), improving to a mean final BCVA of 20/400 (logMAR 1.3, $P=.49$), and mean initial CFT decreased from 318.6 μm to 312.0 μm (final, $P=.96$).

DISCUSSION

The development of optociliary shunt vessels in CRVO has been correlated with better visual acuity outcomes and accelerated resolution of retinal edema. In a study of CRVO eyes treated with radial optic neurotomy, patients with shunt vessels at the neurotomy site had significantly better outcomes ($P<.05$) in visual acuity when compared with patients who did not at 12 months follow-up.¹¹

This retrospective study demonstrated that intravitreal bevacizumab did not prevent the subsequent development of optociliary shunt vessels in patients with CRVO. The incidence of shunt vessel development in our study was 52.9%, and of those patients, 44.4% developed optociliary shunts after intravitreal bevacizumab injection.

In the group 1 patients (those who developed shunt vessels), a greater number of nonischemic CRVO eyes (66.6%) developed shunt vessels than ischemic CRVO eyes (37.4%). Furthermore, while all of the patients in group 1 showed overall improvements from initial to final visits in BCVA ($P=.007$) and CFT ($P=.008$), in separately evaluating the nonischemic and ischemic CRVO subsets, we found that only the nonischemic CRVO eyes in group 1 had statistically significant improvements in CFT, while the ischemic CRVO eyes did not.

In the group 2 patients, there was no significant improvement in BCVA ($P=.23$) or CFT ($P=.89$) in evaluating the group as a whole or when further breaking down the patients into the nonischemic and ischemic CRVO subgroups.

The results of this study indicate that ischemic CRVO may portend a worse outcome due to a decreased tendency toward the development of optociliary shunt vessels. On the other hand, not developing shunt vessels may be a factor influencing whether the CRVO is ultimately ischemic vs nonischemic.

There are limitations to this study, including its retrospective design, small sample size, and a number of confounding variables, including prior treatments with intravitreal triamcinolone injections in more than half of the study patients (52.9%).

This study demonstrated that intravitreal bevacizumab does not prevent the subsequent development of optociliary shunt vessels in patients with CRVO. Furthermore, shunt vessels are correlated with improve-

ments in both anatomic and functional outcomes in CRVO. Future considerations include a retrospective review of all patients included in the Central Vein Occlusion Study and Standard Care versus Corticosteroid for Retinal Vein Occlusion studies to determine the incidence of shunt vessels, the conversion rate from nonischemic CRVO to ischemic CRVO with the development of shunt vessels, and the correlation with treatment outcomes. ■

Aman Shukairy, MD, and Chirag Patel, MD, are both residents at the Wayne State University School of Medicine and Kresge Eye Institute in Detroit.

Christopher Singh, MD, is a retina fellow at the Wayne State University School of Medicine and Kresge Eye Institute in Detroit.

James Puklin, MD, and Tamer H. Mahmoud, MD, PhD, are Assistant Professors, Department of Ophthalmology, Wayne State University School of Medicine and Kresge Eye Institute. Dr. Mahmoud can be reached at +1 313 577 8900; or via e-mail at tmahmoud@med.wayne.edu.



None of the authors have any financial interests to disclose.

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