Long-term Outcomes in Ranibizumab-Treated Patients With Retinal Vein Occlusion; The Role of Progression of Retinal Nonperfusion

RAAFAY SOPHIE, GULNAR HAFIZ, ADRIENNE W. SCOTT, INGRID ZIMMER-GALLER, QUAN DONG NGUYEN, HOWARD YING, DIANA V. DO, SHARON SOLOMON, AKRIT SODHI, PETER GEHLBACH, ELIA DUH, DAVID BARANANO, AND PETER A. CAMPOCHIARO

• PURPOSE: To determine the percentage of ranibizumab-treated patients with retinal vein occlusion (RVO) who had resolution of edema for at least 6 months after the last injection, along with factors and outcomes that correlate with resolution.

• DESIGN: Post hoc analysis of open-label clinical trial.

• METHODS: Twenty patients with branch RVO (BRVO) and 20 with central RVO (CRVO) received ranibizumab monthly for 3 months and as needed for recurrent/persistent macular edema, no more frequently than every 2 months. Patients still requiring injections after month 40 received scatter and grid laser photocoagulation to try to reduce the need for injections. Main outcome measures included the percentage of patients who had resolution of edema, change in best-corrected visual acuity (BCVA) from baseline, and change in area of retinal nonperfusion in central subfields.

• RESULTS: Nine patients with BRVO (45%) had edema resolution from injections alone after a mean of 20.2 months, 4 resolved after addition of laser, 4 were unresolved through 72 months, and 3 exited prior to resolution. Five patients with CRVO (25%) resolved from injections alone after a mean of 14.0 months, 8 remained unresolved through 72 months despite addition of laser, and 7 exited prior to resolution. For BRVO or CRVO, there was a negative correlation between posterior retinal nonperfusion area and BCVA at months 18, 24, and 36 ($P < .05$).

• CONCLUSIONS: In patients with RVO, infrequent ranibizumab injections to control edema may not be sufficient to prevent progression of retinal nonperfusion, which may contribute to loss of visual gains. (Am J Ophthalmol 2013;156:693–705. © 2013 by Elsevier Inc. All rights reserved.)

AJO.com Supplemental Material available at AJO.com.

Accepted for publication May 28, 2013.

From the Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Quan Dong Nguyen and Diana V. Do are currently affiliated with the Stanley M. Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, Nebraska.

David Baranano is currently affiliated with Retina Specialists, Towson, Maryland.

Inquiries to Peter A. Campochiaro, Maumenee 719, The Wilmer Eye Institute, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287-9277; e-mail: pcampo@jhmi.edu

RETINAL VEIN OCCLUSION (RVO) CONSISTS OF central RVO (CRVO) and branch RVO (BRVO), which are prevalent retinal vascular diseases. In patients with CRVO, thrombosis of the main outflow vessel of the retina results in variable amounts of hemorrhage, edema, and retinal nonperfusion throughout the retina, whereas in patients with BRVO there is occlusion of a proximal branch of the central retinal vein that results in similar findings throughout about half of the retina. Hemorrhages and edema were assumed to be attributable to elevated intraluminal pressure, but the development of ranibizumab (Lucentis; Genentech, Inc, South San Francisco, California, USA), a Fab fragment that specifically binds all isoforms of vascular endothelial growth factor A (VEGF), made it possible to test the hypothesis that VEGF contributes to the edema, and the hypothesis was found to be correct.[1] This has been confirmed by the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO)[2] and Treatment of Macular Edema following Central Retinal Vein Occlusion: Evaluation of Efficacy and Safety (CRUISE)[3] trials. In BRAVO, monthly injections of 0.3 or 0.5 mg ranibizumab for 6 months resulted in gains in mean letter score from baseline BCVA of 16.6 and 18.3, compared to 7.3 in the sham injection group.[2] In CRUISE, at the month 6 primary endpoint, there was a mean improvement from baseline in BCVA letter score of 12.7 (0.3 mg) and 14.9 (0.5 mg) vs 0.8 (sham).[3] These gains were maintained between months 6 and 12 by intermittent injections of ranibizumab for recurrent/persistent edema.[4,5] Thus, in patients with RVO, blockade of VEGF with ranibizumab reduces edema and improves vision. Monthly injections of ranibizumab also resulted in more rapid resolution of retinal hemorrhages than sham injections, indicating that high levels of VEGF contribute to retinal hemorrhages as well as macular edema.[4,5]

These outcomes are outstanding, and it was hoped that they would be maintained and the need for injections would be eliminated as collaterals developed and circumvented the obstruction. However, 2-year follow-up of

0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2013.05.039

patients entered in the original ranibizumab study[1] showed that many patients with BRVO or CRVO still required injections for chronic, recurrent macular edema and that injection only as frequently as every 2 months allowed maintenance of early visual gains in patients with BRVO, but was associated with some reduction in visual gains in patients with CRVO.[6] Findings were similar in the much larger HORIZON trial, in which after 12 months of treatment with ranibizumab in BRAVO and CRUISE, patients with RVO were seen at least every 3 months and given an injection of ranibizumab for recurrent/persistent macular edema.[7] These data suggest that many patients with RVO still require frequent anti-VEGF injections 24 months after the onset of treatment and that long-term outcomes are unknown. We now report long-term outcomes for patients with RVO enrolled in the original ranibizumab study.[1]

SUBJECTS AND METHODS

THE FOCUS OF THIS REPORT IS LONG-TERM FOLLOW-UP OF a study[1,6] that was approved by the institutional review board (IRB) of Johns Hopkins University School of Medicine. The study was registered on December 1, 2006 at www.clinicaltrials.gov (NCT00407355) and conducted in compliance with the Declaration of Helsinki, US Code 21 of Federal Regulations, and the Harmonized Tripartite Guidelines for Good Clinical Practice (1996). All patients provided informed consent before participation in the study. Twenty patients with BRVO and 20 patients with CRVO were randomized 1:1 to receive either 0.3 mg or 0.5 mg ranibizumab monthly for 3 months. Patients were seen at months 4, 5, 6, 9, and 12, and an attempt was made to hold injections to determine whether a period of rebound edema would be followed by final resolution of edema, but if edema persisted for several months and there was concern that it was a threat to the patient's long-term visual potential, an injection of 1.25 mg bevacizumab was allowed. Beginning at month 12, patients were seen every 2 months and given an injection of ranibizumab if time-domain optical coherence tomography (OCT) demonstrated recurrent edema involving the fovea. Three patients with CRVO reached the month 12 visit before the approval of the amendment allowing for ranibizumab injections and received an injection of bevacizumab at month 12. Beginning at month 40, in addition to being eligible for as-needed treatment with ranibizumab, patients with evidence of recurrent macular edema by OCT underwent ultra-widefield fluorescein angiography and received scatter laser photocoagulation to all areas of retinal nonperfusion outside the fovea, followed by an injection of ranibizumab. If edema persisted and required 2 consecutive injections after laser treatment, ultra-widefield fluorescein angiography was repeated and supplemental scatter laser photocoagulation was done along with grid laser to areas of leakage in the macula but outside the foveal avascular zone. This was also followed by an injection of ranibizumab.

At each study visit the patient had best-corrected visual acuity (BCVA) measured by an experienced examiner using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol,[8] OCT performed by an experienced investigator with a Stratus OCT3 (Carl Zeiss Meditec, Dublin, California, USA) using the Fast Macular Scan protocol, and a complete eye examination. Serial 7-field fluorescein angiography (FA) and color fundus photographs using a 30-degree lens were performed at baseline and at months 1, 3, 4, 18, 24, 30, and 36. Ultra-widefield FAs using the Optos P200Tx (Optos, Dunfermline, Scotland) were performed at the first study visit after month 36, on each visit in which laser treatment was given, and at months 48 and 60.

• **ADMINISTRATION OF STUDY DRUG:** Povidone-iodine was used to clean the lids and a lid speculum was inserted. Topical anesthesia was applied and the conjunctiva was irrigated with 5% povidone-iodine. A 30-gauge needle was inserted through the pars plana and 0.05 mL ranibizumab was injected into the vitreous cavity. Funduscopic examination was done to confirm retinal perfusion.

• **LASER PHOTOCOAGULATION:** Areas of retinal nonperfusion were treated with 200- to 500-μm burns 1 burn width apart. It was also assumed that there was additional nonvisualized retinal nonperfusion in the far periphery and 5 rows of laser photocoagulation were given for 360 degrees for patients with CRVO and roughly 180-200 degrees for patients with BRVO (the 2 quadrants affected by the BRVO) starting just posterior to the aura serrata. An injection of ranibizumab was given after completion of the laser photocoagulation and the patient was seen every 2 months and treated with ranibizumab if there was recurrent/persistent macular edema. If a ranibizumab injection was required on 2 consecutive visits after laser, supplemental laser photocoagulation was given to provide complete scatter photocoagulation of the peripheral retina to within 2 disc diameters of the arcade vessels and grid laser photocoagulation (100-μm burns 1 burn width apart) was given to areas of diffuse leakage in the macula but outside the foveal avascular zone. An injection of ranibizumab was given after the laser. If injections of ranibizumab were needed on 2 consecutive visits after the second laser treatment, remaining retina outside the arcade vessels was treated, followed by an injection of ranibizumab. Patients were then seen every 2 months and treated with ranibizumab for recurrent edema.

• **MEASUREMENT OF AREA OF POSTERIOR RETINAL NONPERFUSION:** Areas of retinal nonperfusion were