Peripheral Ischemia and Rebound Edema in RVO

In some patients, a different approach may be needed to break the rebound cycle.

BY MICHAEL A. SINGER, MD; COLIN S. TAN, MBBS, FRCSED (OPHTH), MMED (OPHTH); AND SRINIVAS R. SADDA, MD

Until the past few years, when pharmacologic treatments for central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) became available, the standard of care for macular edema secondary to CRVO was observation. Since US Food and Drug Administration (FDA) approval of the dexamethasone intravitreal implant (Ozurdex, Allergan Inc.) and ranibizumab (Lucentis, Genentech) for treatment of CRVO and BRVO, physicians have been presented with expanded treatment options.

Because retinal vein occlusions (RVOs) can have a varied natural history, however, an underlying challenge in managing macular edema secondary to RVO, particularly CRVO, is how to know when to stop treatment. One of the consequences of discontinuing therapy prematurely is rebound edema, which is often worse than the initial swelling.

One of the consequences of discontinuing therapy prematurely is rebound edema, which is often worse than the initial swelling.

PROSPECTIVE STUDY

In an effort to find a potential mechanism to explain and address this phenomenon of rebound edema, my colleagues and I conducted an institutional review board-approved, investigator-sponsored study.[1] One of the mechanisms that we proposed as the driving force for rebound edema was peripheral ischemia. Because peripheral ischemia generally cannot be seen on fluorescein angiography, which covers between 30-50º of the posterior pole, we used widefield angiography to gain a better ability to image the periphery and see the amount of ischemia present.

A number of studies have suggested that, although some retinal pathologies may seem to be a limited process confined to the area of the posterior pole, they may in fact be significantly more widespread; this is specifically so in diabetes[2-5] but also to a smaller extent in RVO.

Our study included a group of patients with BRVO or CRVO seen at Medical Center Ophthalmology Associates in San Antonio, TX, who had undergone therapy with intravitreal injections of anti-VEGF and/or the dexamethasone intravitreal implant. At all visits, we

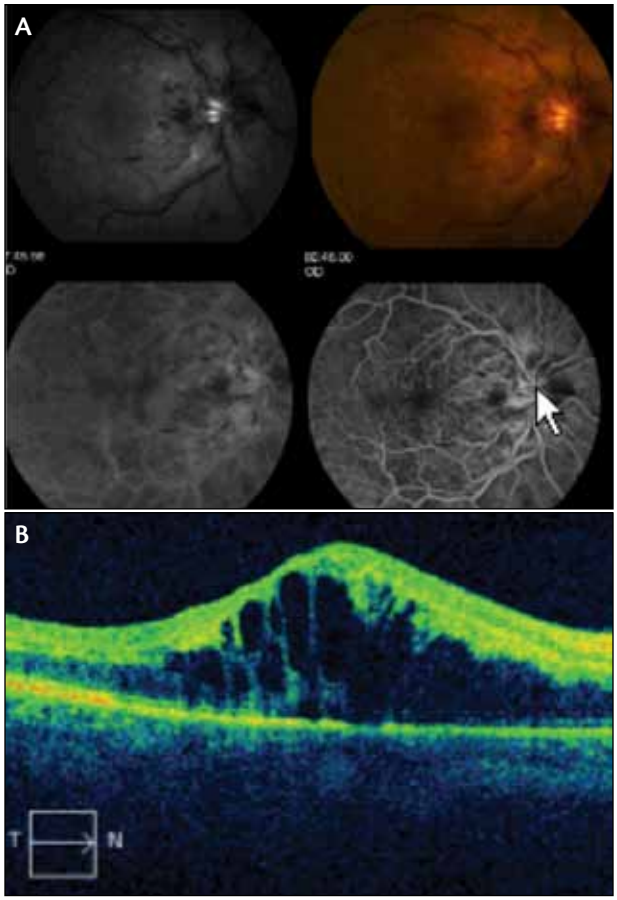

Figure 1. A 72-year-old man presented with CRVO and count fingers vision. Fundus and fluorescein angiography (FA) images showed areas of ischemia (A), and optical coherence tomography (OCT) indicated central subfield thickness (CST) of 768 µm (B). The patient was given an injection of ranibizumab.

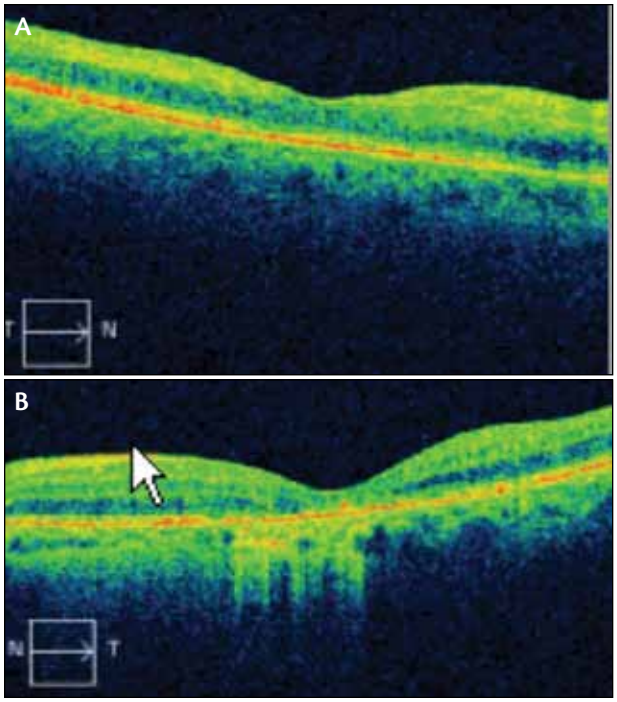

Figure 2. Two weeks later, the patient's vision improved to 20/400 and CST decreased to 241 µm (A). At this visit, he received dexamethasone intravitreal implant, and his OCT decreased further to 226 µm (B).

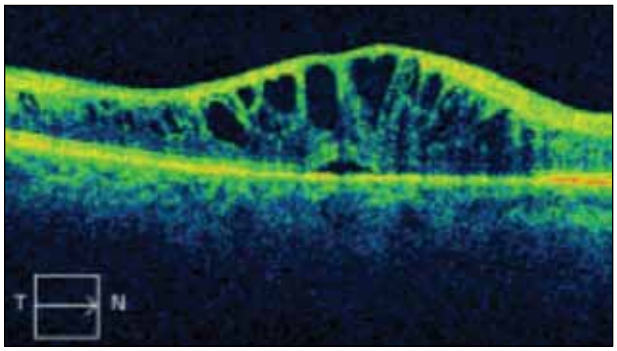

Figure 3. Four months later, the patient's vision decreased back to count fingers, and his OCT increased to 595 µm.

obtained 200° widefield angiographies with the Optos 200Tx and spectral domain optical coherence tomography (OCT) with the Cirrus HD-OCT (Carl Zeiss Meditec) to determine differences between when their edema cleared and when it rebounded. We enlisted masked investigators at the Doheny Reading Center to read the images and measure the areas of ischemia using their GRADOR validated software. The GRADOR software was used to calculate the area of ischemia as a percentage of the total area of the image (the ischemic index).

In 32 patients in the study, the mean age was 76 years, and the mean area of retinal ischemia was 14.8% (range, 0% to 67.7%, standard deviation ±17.3). In 17 patients, the ischemic index was 10% or less, and in 15, it was greater than 10%. The areas of nonperfusion were greater when macular edema was present compared with when it had resolved (14.8% vs 10.2%; $P < .001$). In eyes with macular edema, central subfield thickness (CST) on OCT showed a trend to be thicker in those with an ischemic index greater than 10%, compared with those with ischemic index of 10% or less. The decrease in CST in response to treatment also showed a trend to be greater in those with ischemic index greater than 10%.

This investigation showed that patients with BRVO and CRVO demonstrate considerable variability in the extent of peripheral retinal nonperfusion at baseline and that this seems to affect the amount of retinal edema and the anatomic and functional response to treatment. We hypothesized that larger areas of peripheral retinal non-

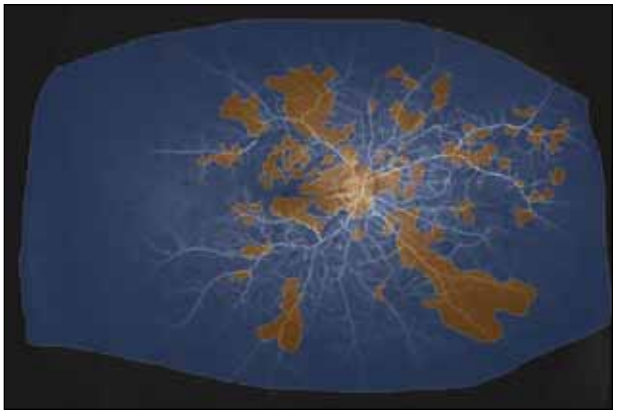

Figure 4. Widefield fluorescein angiography (FA) showed significant ischemia covering 86.80% of the area imaged, and the patient received another ranibizumab injection. The blue areas of the image show ischemia and the orange areas show perfusion.

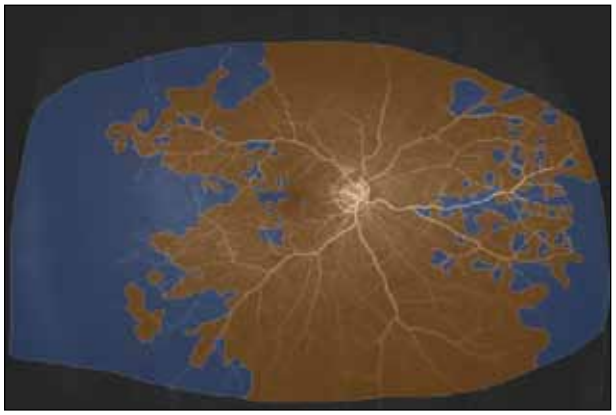

Figure 5. Two weeks after the second injection of ranibizumab, the patient's vision increased to 20/400, and CST decreased to 197 µm. Widefield FA image showed a reduction in the area of ischemia to 39.08%. The blue areas of the image show ischemia and the orange areas show perfusion.

perfusion may drive VEGF production and result in more severe macular edema. In some of the more severe cases, we observed the development of rubeosis, a condition in which the VEGF levels are so high that there is not only edema but also the formation of new blood vessels.

CASE STUDY

In this study, we observed that circulation improved after anti-VEGF injection in patients with rebound edema.

A 72-year-old man presented with CRVO and count fingers vision. Fundus and fluorescein angiography (FA) images (Figure 1A) showed areas of ischemia, and OCT indicated a CST of 768 µm (Figure 1B). The patient was given an injection of ranibizumab.

Two weeks later, the patient's vision had improved to 20/400, and his CST decreased to 241 µm (Figure 2A). At this visit, he received the dexamethasone intravitreal implant, and his OCT decreased further to 226 µm (Figure 2B).

Four months later, the patient's vision decreased back to count fingers, and CST increased to 595 µm (Figure 3). Widefield FA showed significant ischemia covering 86.80% of the area imaged (Figure 4), and the patient received another ranibizumab injection.

Two weeks after the second injection of ranibizumab, the patient's vision had increased to 20/400, and CST decreased to 197 µm. The widefield FA image showed a reduction in the area of ischemia to 39.08% (Figure 5).

AN ANALOGY

In conceptualizing rebound edema after the treatment of peripheral ischemia in CRVO, one might make

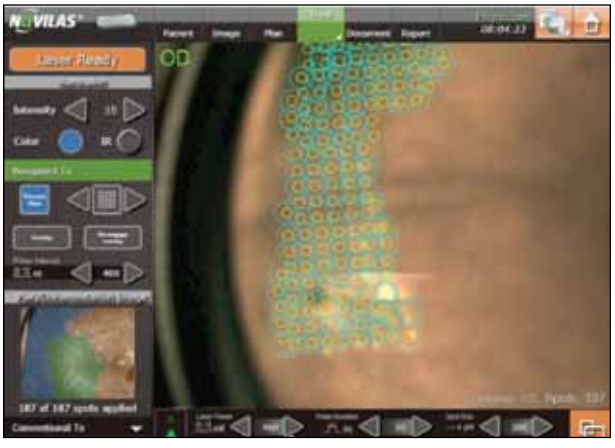

Figure 6. Laser using integrated images from both Optos and Navilas laser systems.

Figure 7. Final pattern for temporal quadrant. A similar process is to be repeated for other quadrants.

> Decreasing the VEGF load with targeted PRP rather than anti-VEGF therapy might be what is needed to stop the cycle of ischemia in these patients.

an analogy to caring for grass in a time of drought. Grass can appear in 1 of 3 colors: green, yellow, or brown. How do we manage each state? Green is straightforward: The grass is healthy, and you maintain it. Yellow grass is more complicated because it is difficult to predict whether it will live or die with watering. Some will turn green again, and some, despite watering, will become brown and die. Brown grass again is straightforward: It is dead; why waste water on brown grass, assuming that there is a limited water supply in drought conditions?

Following this analogy, patients with CRVO have 3 areas. They have a well-perfused area similar to the green grass. There are ischemic peripheral areas that never recover, despite repeated anti-VEGF injections (brown grass). The theory is with brown grass, (especially assuming a limited water supply), removing the grass (via targeted panretinal photocoagulation [PRP]) might decrease the amount of water that is diverted. Between these extremes, there are areas that may derive benefit from treatment, like the yellow grass (reversible ischemia, which can be identified via response to anti-VEGF injections). By performing targeted PRP, the least amount of peripheral vision is sacrificed. Hopefully, the feedback loop of upregulating VEGF due to ischemia is halted and rebound edema is eliminated. In this case, the patient received anti-VEGF injections and sustained-release steroid treatment, and his condition initially improved, but then months later, the edema recurred as the treatment effect wore off.

CONCLUSIONS

How can our ability to image the peripheral circulation ultimately help us to manage RVO patients such as these? Our goal is to stop the cycle of ischemia. Rather than give repeated anti-VEGF injections and continue to see regression and then the return of ischemia, is there something we can do to stop the cycle?

We believe that targeted panretinal photocoagulation (PRP) may help to break this cycle in patients with rebound edema in RVO. By examining widefield images for areas of ischemia, perhaps using software similar to that described in this article, we can identify areas of "brown grass" that will always be ischemic, that will not respond to "watering" with anti-VEGF therapy, but that might respond to targeted PRP. Decreasing the VEGF load with targeted PRP rather than anti-VEGF therapy might be what is needed to stop the cycle of ischemia in these patients. We are starting to use a combination of the Optos images as well as the Navilas laser system (OD-OS) to laser the peripheral retina in a systematic manner to ensure both consistent spot size and spacing as well as precise anatomic location to preserve as much peripheral retina as possible (Figures 6 and 7). ■

Michael A. Singer, MD, is the Managing Partner and Director of Clinical Trials at Medical Center Ophthalmology Associates in San Antonio, TX. He is also Assistant Clinical Professor at the University of Texas Health Science Center of San Antonio. Dr. Singer states that he has received research funding from Genentech, Regeneron, NeoVista, Macusight, Allergan, Alcon, and Thrombogenics, and has been a consultant to Allergan, ISTA, Alcon Laboratories Inc., and Genentech. He may be reached at msinger@mcoaeyecare.com.

Colin S. Tan, MBBS, FRCSEd (Ophth), MMed (Ophth), is a Consultant Ophthalmologist and Clinician Researcher with the Department of Ophthalmology, Tan Tock Seng Hospital (National Healthcare Group Eye Institute) in Singapore. Dr. Tan states that he has no financial relationships to disclose. He may be reached at colintan_eye@yahoo.com.sg.

Srinivas R. Sadda, MD, is an Associate Professor of Ophthalmology at the Doheny Eye Institute and University of Southern California in Los Angeles. Dr. Sadda states that he shares in royalties from intellectual property licensed to Topcon Medical Systems from Doheny Eye Institute and has served as a consultant to Heidelberg Engineering. The Doheny Eye Center and Dr. Sadda have received research support from Carl Zeiss Meditec and Optos. The Doheny Eye Center has received research support from Optovue, Inc. He may be reached at ssadda@doheny.org.

1. Tan CS, Singer M, Bell D, Sadda SR. Predictive value of the area of peripheral retinal non-perfusion on treatment response in branch and central retinal vein occlusion. Paper presented at: Association for Research in Vision and Ophthalmology annual meeting; May 7, 2012; Fort Lauderdale, FL.
2. Gardner TW, Eller AW, Friberg TR. Reduction of severe macular edema in eyes with poor vision after panretinal photocoagulation for proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol.* 1991;229(4):323-328.
3. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. *Br J Ophthalmol.* 2012;96(5):694-698.
4. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S. Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. *Retina.* 2012;32(4):785-791.
5. Spaide RF. Peripheral areas of nonperfusion in treated central retinal vein occlusion as imaged by wide-field fluorescein angiography. *Retina.* 2011;31(5):829-837.