USE OF THE ISCHEMIC INDEX ON WIDEFIELD FLUORESCEIN ANGIOGRAPHY TO CHARACTERIZE A CENTRAL RETINAL VEIN OCCLUSION AS ISCHEMIC OR NONISCHEMIC

AKSHAY S. THOMAS, MD, MS,* MRIDUL K. THOMAS, PHD,† AVNI P. FINN, MD, MBA,* SHARON FEKRAT, MD*

Purpose: To understand the relationship between baseline ischemic index (IsI) values on ultra-widefield fluorescein angiography and classification as ischemic central retinal vein occlusion (CRVO).

Methods: Single-center retrospective cohort study of CRVO patients imaged using ultra-widefield fluorescein angiography from which IsI values were calculated. An ischemic CRVO was defined as those eyes with an afferent pupillary defect and counting fingers acuity or worse or neovascularization during the first year of follow-up. Logistic regression was performed to characterize the relation between the IsI and clinical outcomes.

Results: Sixty eyes of 60 treatment-naive CRVO patients with baseline ultra-widefield fluorescein angiography and ≥1 year of follow-up were identified. Those with an IsI ≥35% were significantly more likely to have an ischemic CRVO during the first year of follow-up than those with an IsI <35% (83.3 vs. 13.9%, odds ratio 111, $P < 0.0001$). Baseline and final logarithm of the minimum angle of resolution acuity were worse in eyes with an IsI ≥35% (1.18 vs. 0.46, $P < 0.001$ and 1.26 vs. 0.45, $P < 0.001$, respectively) despite similar baseline and final central subfield thickness ($P = 0.1–0.23$).

Conclusion: A baseline IsI of ≥35% on ultra-widefield fluorescein angiography in eyes with treatment-naive CRVO was sensitive (90%) and specific (92.5%) for classification as an ischemic CRVO during the first year of follow-up.

RETINA 0:1–6, 2018

Central retinal vein occlusion (CRVO) is a common cause of visual impairment in adults. A CRVO may be classified as ischemic or nonischemic, each of which confers a different prognosis.[1] Although both variants can cause significant visual impairment from macular edema, ocular neovascularization is only considered a consequence of the ischemic form.[2,3] Patients presenting with a nonischemic CRVO are at risk of subsequently converting to an ischemic CRVO. In a study of 442 eyes with nonischemic CRVO at presentation, the rate of conversion to an ischemic CRVO was found to be 13.2% at 6 months and 18.6% at 18 months in patients aged 65 years and older.[3]

The designation as an ischemic or nonischemic CRVO was historically made based on findings on nonwidefield fluorescein angiography (FA). Until the Central Vein Occlusion Study in the 1990s, an ischemic CRVO was commonly defined as one in which there was greater than 10 disk areas of retinal capillary nonperfusion on FA. The Central Vein Occlusion Study found that CRVO eyes with less than 10 to 15 disk areas of nonperfusion were at low risk of developing neovascularization of the iris or

From the *Department of Ophthalmology, Duke University, Durham, North Carolina; and †Department of Aquatic Ecology, Eawag: Swiss Federal Institute of Aquatic Science and Technology, Dübendorf, Switzerland.

Unrestricted Grant from Research to Prevent Blindness, New York, NY. Heed Ophthalmic Fellowship award to A. P. Finn from Heed Ophthalmic Foundation, San Francisco, CA.

None of the authors has any financial/conflicting interests to disclose.

Reprint requests: Sharon Fekrat, MD, Department of Ophthalmology, Duke University, 2351 Erwin Road, Box 3802, Durham, NC 27710; e-mail: fekra001@mc.duke.edu

angle but there was a linear increase in that risk with increasing disk areas of nonperfusion.[4] Pivotal work by Hayreh et al[5] found that functional tests such as visual acuity, presence of an afferent pupillary defect (APD), visual fields, and electroretinography were superior to morphologic tests such as ophthalmoscopy and FA in determining whether an acute CRVO is ischemic or not in a large cohort. Specifically, they found that 94% of patients with an ischemic CRVO had an APD of >0.9 log units. Additionally, 93% of patients with vision of 20/400 or worse had an ischemic CRVO. The potential limitation of these studies is that angiographic data relied on traditional fundus viewing cameras with a field of view ranging from 30° to 50°, which would not allow for adequate examination of the retinal periphery.

The Optos fundus camera (Optos PLC, Dunfermline, Scotland) allows for ultra-widefield fluorescein angiography (UWFFA) providing a 200° field of view in a single image.[6] Studies have shown that knowledge of the precise area of nonperfusion is important in the management of retinal vascular disease.[7–10] Prasad et al[7] found an association between untreated nonperfusion on UWFFA and neovascularization as well as macular edema in branch RVO and hemi-RVO. Additionally, Singer et al[8] found that the degree of peripheral nonperfusion on UWFFA correlated with severity of macular edema and treatment response in eyes with CRVO. Given the developing clinical utility of UWFFA in management of RVO, this study aimed to elaborate on whether findings on UWFFA can help determine whether a CRVO is ischemic or will become ischemic in the short term.

Methods

Patient Selection

After approval by the Duke Institutional Review Board, the Duke Enterprise Data Unified Content Explorer system was used to identify patients diagnosed with a CRVO between January 1, 2009, and July 1, 2016. Charts were reviewed and only those who were treatment naive with baseline UWFFA and at least 1 year of follow-up were included.

Chart Review

Data from the charts of study participants including age at time of CRVO diagnosis, race, gender, cardiovascular comorbidities, ocular comorbidities, visual acuity, ophthalmic examination findings, treatment history, findings on UWFFA, and spectral domain optical coherence tomography were abstracted.

Ultra-Widefield Fluorescein Angiography Review

All UWFFA were performed using the Optos 200Tx fundus camera. A representative arteriovenous, midphase, and late FA image as well as a widefield pseudocolor photograph were selected for each study participant. If the image quality was inadequate, the patient was excluded from the study. Midphase UWFFA images were deidentified and graded for ischemic index (IsI) values as done in previous studies[9,11] by two masked graders (A.S.T. and A.P.F.). Briefly, the image was imported into Adobe Photoshop and parameters such as contrast and brightness were adjusted to ensure that there were not additional subtle capillary networks visible beyond an apparent perfused/nonperfused junction. Nonperfused pixels were measured (Figure 1) and divided by the total area of gradable pixels corresponding to the fundus. The value was multiplied by 100 to arrive at the IsI value expressed as a percentage. For all images, areas of potential blockage from hemorrhage were excluded from the analysis by comparing midphase FA images with the pseudocolor photographs. Discordant grades (>2% gross difference in IsI value) were discussed between graders and a consensus value was finalized.

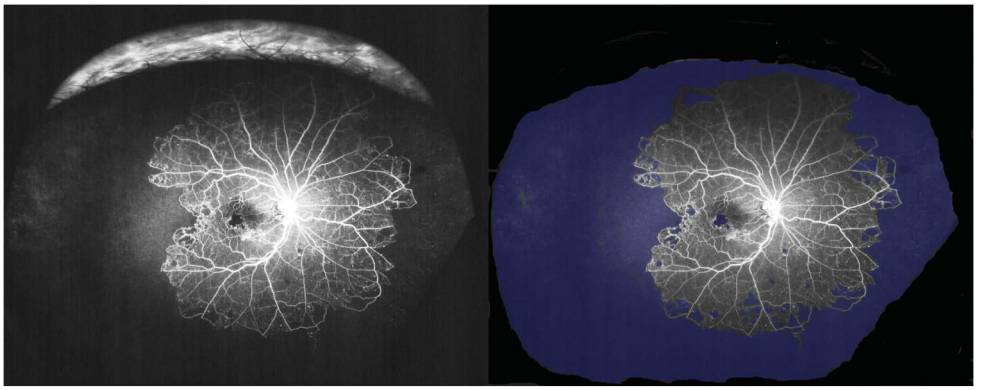

Fig. 1. Representative UWFFA of an eye with a CRVO included in this study. Midphase UWFFA images were analyzed for areas of nonperfusion (left). The percentage of pixels representing the fundus which were nonperfused (blue) were measured (right).

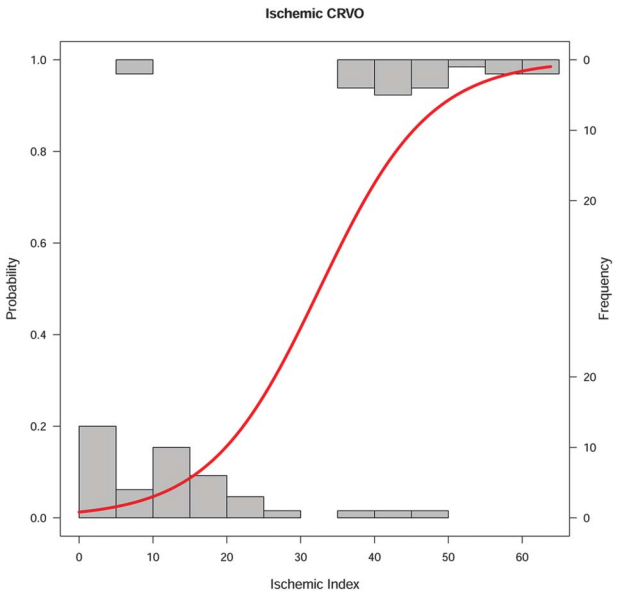

Fig. 2. Logistic regression curve showing probability of having or developing an ischemic CRVO during the first year of follow-up as a function of baseline IsI value. The top histogram shows the frequency of patients with ischemic CRVO for a given IsI range. The bottom histogram shows the frequency of patients with nonischemic CRVO for a given IsI range.

The final IsI value was the average of the two graders' measurements for concordant values. Additional FA findings such as foveal avascular zone enlargement on the arteriovenous image and presence of neovascularization on the late phase image were reviewed separately by a single masked grader (A.S.T.).

Defining an Ischemic Central Retinal Vein Occlusion Based on Functional Data

A patient was defined as having an ischemic CRVO if they had 1) counting fingers vision not attributable to a media opacity in addition to an APD confirmed by a physician or 2) evidence of anterior segment or posterior segment neovascularization not attributable to another disease. A CRVO was considered ischemic if either of these criteria was met at any point during the first year of follow-up.

Statistical Analysis

We used logistic regression to calculate the probability of being classified as an ischemic CRVO during the first year of follow-up based on the IsI value. We subsequently defined two groups of individuals based on an IsI threshold identified from this logistic regression analysis. We used chi-square tests to compare the prevalence of risk factors (glaucoma, hypertension, diabetes, smoking, and hyperlipidemia) between the two groups. *P*-values for the chi-square tests were calculated using 10,000 replicate Monte Carlo simulations. We used *t* tests to compare the two groups' distributions of: 1) baseline visual acuity, 2) final visual acuity, 3) baseline macular thickness, and 4) final macular thickness.

We used logistic regression to calculate the odds ratios (ORs) of the 2 groups' incidence of: 1) having an ischemic CRVO, and 2) having vision of 20/200 or worse. Because this approach ignores valuable information by discretizing a continuous variable, we also used an alternate approach that analyzed IsI as a continuous variable. We performed logistic regressions to calculate the probability of having an ischemic CRVO, and of having vision of 20/200 or worse, as a function of the continuous variable IsI. Data analysis was conducted in the R statistical environment v. 3.4.0.

Results

Patient Characteristics

We identified 60 eyes of 60 patients with treatment-naive CRVO with baseline UWFFA imaging and at least 1 year of follow-up. The mean age at onset of CRVO was 61.2 years (range 28–89 years). Thirty-eight patients were male. All patients had at least 1 classic risk factor for CRVO such as hypertension, diabetes, smoking, glaucoma, and hyperlipidemia and 22 patients had 2 or more risk factors.

Clinical Outcomes

Mean baseline logarithm of the minimum angle of resolution (logMAR) acuity was 0.71 (Snellen equivalent ~20/100, SD 0.64). The mean follow-up time was 22.2 ± 11.2 months. Final acuity was 0.6 (Snellen equivalent 20/80, SD 0.73). The mean number of intravitreal anti–vascular endothelial growth factor (anti-VEGF) injections was 6.8 ± 3.6 in the first year. Baseline central subfield thickness (CST) was 488.8 ± 286.4 μm and final CST was 313.4 ± 148.9 μm. 15/60 eyes (25%) met criteria for being an ischemic CRVO at baseline and an additional 6/45 eyes (13.3%) that were nonischemic at baseline converted to an ischemic CRVO within the first year of follow-up. The mean IsI value was 22.43% (SD 19.35, range 0–63.9%). The intergrader agreement for IsI calculations was 96.7%.

Clinical Outcomes Based on Ischemic Index

Logistic regression revealed an increasing probability of being classified as an ischemic CRVO during the first year of follow-up with increasing IsI values (Figure 2). The logistic regression curve showed that the probability of having an ischemic CRVO was close

Table 1. Clinical Outcomes Based on IsI

	IsI ≥35% (N = 21/60)	IsI <35% (N = 39/60)	
Mean baseline CST ± SD (μm)	584.8 ± 340.2	439.5 ± 244.9	$P = 0.1$
Mean final CST ± SD (μm)	374.2 ± 222.8	239.1 ± 101.9	$P = 0.23$
Baseline mean logMAR acuity	1.18	0.46	**$P < 0.001$**
Final mean logMAR acuity	1.26	0.45	**$P < 0.001$**
Percentage with final vision 20/200 or worse	N = 10/21, 47.6%	N = 5/39, 12.8%	**$P = 0.004$; OR 6.2**
Percentage with ischemic CRVO	N = 18/21, 83.3%	N = 2/39, 13.9%	**$P < 0.0001$; OR 111**

Bold values indicate statistical significance for alpha = 0.05.

to 50% when the baseline IsI was 35%. Study participants were grouped based on baseline IsI: those with an IsI <35% (39/60 patients, 65%) and those with an IsI ≥35% (21/60 patients, 35%), and clinical outcomes were compared.

Baseline characteristics such as age, sex, race, CRVO risk factors, and frequency of use of blood thinners were similar between the groups. The mean duration of follow-up was similar between those with an IsI <35% and those with an IsI ≥35% (22.5 ± 12.2 vs. 21.8 ± 10.8 months, $P = 0.94$). Baseline and final CST were not significantly different between those with an IsI <35% and those with an IsI ≥35% (439.5 ± 244.9 vs. 584.8 ± 340.2 μm, $P = 0.1$ and 239.1 ± 101.9 vs. 374.2 ± 222.8 μm, $P = 0.23$, respectively). Baseline and final choroidal thickness were similar between the groups ($P = 0.31$–0.96). The proportion of patients with baseline cystoid macular edema was similar between the groups ($P = 0.95$). Those with an IsI <35% received a similar number of intravitreal injections to those with an IsI ≥35% over the first year of treatment (6.4 ± 3.2 vs. 7.2 ± 4.1 injections, $P = 0.87$).

Baseline logMAR acuity was worse for those with an IsI ≥35% (1.18 vs. 0.46; Snellen equivalent 20/300 vs. 20/58; $P < 0.001$) (Table 1). Those eyes with an IsI ≥35% were significantly more likely to have or convert to an ischemic perfusion status during the first year than those with an IsI <35% (18/21 patients, 83.3% vs. 2/39 patients, 13.9%, OR 111 [confidence interval: 20.9–988], $P < 0.0001$). The sensitivity and specificity of classifying a CRVO as ischemic based on an IsI ≥35% was 90% and 92.5%, respectively. The positive predictive value and negative predictive value of classifying a CRVO as ischemic based on an IsI ≥35% was 86% and 95%, respectively.

A significantly greater proportion of those with IsI ≥35% had an enlarged foveal avascular zone (64.7 vs. 17.5%, $P = 0.0005$). Final logMAR acuity was worse in those eyes with an IsI ≥35% (1.26 vs. 0.45; Snellen equivalent 20/364 vs. 20/56; $P < 0.001$). Patients with an IsI ≥35% were more likely to have final acuity of 20/200 or worse (10/21 patients, 47.6% vs. 5/39 patients, 12.8%; OR 6.2 [confidence interval: 1.8–23.8]; $P = 0.004$) (Figure 3).

Discussion

Classification of a CRVO as ischemic or non-ischemic is important because the two entities confer a greatly different risk of development of ocular neovascularization and neovascular glaucoma. Natural history studies before the anti-VEGF era noted rates of ocular neovascularization from 14% to as high as 50% in untreated CRVO with a mean duration of onset of 6 months from the time of CRVO onset.[2–4] Data from eyes undergoing serial anti-VEGF therapy for cystoid macular edema associated with CRVO have shown rates of ocular neovascularization as low as 0%.[12,13]

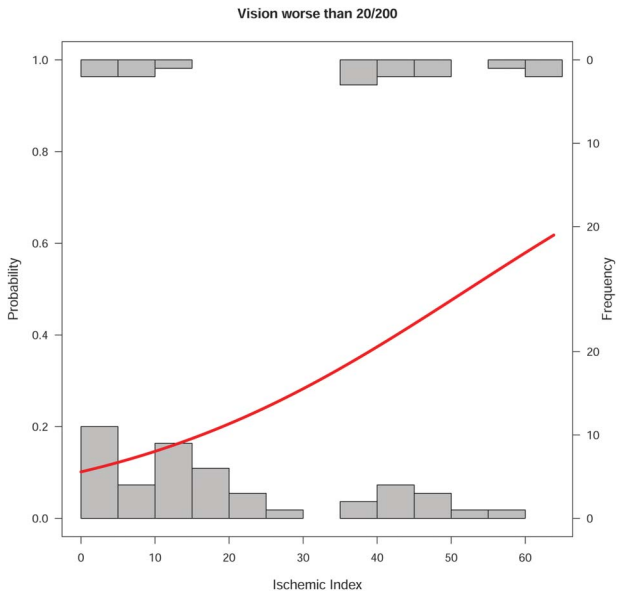

Fig. 3. Logistic regression curve showing probability of having 20/200 or worse vision at final follow-up as a function of baseline IsI. The top histogram shows the frequency of patients with final visual acuity of 20/200 or worse for a given IsI range. The bottom histogram shows the frequency of patients with final visual acuity better than 20/200 for a given IsI range.

In everyday practice, however, ocular neovascularization is still a complication seen in eyes with CRVO. DeCroos et al[14] reported on a series of patients undergoing anti-VEGF treatment for CRVO-associated cystoid macular edema who developed ocular neovascularization. They found that the mean duration of onset of neovascularization was 17.0 ± 10.3 months after CRVO onset. Importantly, the authors noted that the treatment-free interval before onset of neovascularization was 6.2 ± 7.3 months. Thus, extension of treatment intervals or cessation of anti-VEGF therapy altogether may be complicated by neovascular sequelae and classification of a CRVO as ischemic or nonischemic remains important.

Although FA was traditionally used to classify a CRVO as ischemic or nonischemic, it has since been replaced with other functional and morphologic tests as we outlined earlier. This was in large part due to an inadequate sampling of the retina by traditional fundus cameras. In this study, we correlated the IsI on UWFFA with clinical outcomes in CRVO and thus aimed to highlight the continued importance of FA in the management of CRVO.

We initially calculated the probability of having an ischemic CRVO during the first year after CRVO onset as a function of the IsI using logistic regression. We found that an IsI of approximately 35% conferred a 50% probability of classification as an ischemic CRVO during this timeframe. We subsequently analyzed clinical outcomes based on whether the IsI was $<35\%$ or $\geq 35\%$. There was a nonsignificant trend for eyes with an IsI $\geq 35\%$ to have greater baseline and final CST. This is in keeping with a study by Singer et al in which they noted a correlation between the baseline amount of peripheral nonperfusion with baseline CST in eyes with branch RVO or CRVO.[5] This is likely due to higher levels of circulating VEGF and other cytokines in eyes with greater amounts of capillary nonperfusion as has been suggested in other studies.[8,10,11]

Patients with an IsI $\geq 35\%$ were over 100 times more likely to be classified as an ischemic CRVO during the first year of follow-up compared with those with an IsI $<35\%$. Tsui et al evaluated the IsI in eyes with CRVO presenting with ocular neovascularization. These eyes had a mean IsI of 75% with all eyes having an IsI $>45\%$.[9] In our study, we included the additional functional parameters of visual acuity and presence of an APD to help define an ischemic CRVO. Because only close to half of eyes with an ischemic CRVO develop ocular neovascularization, inclusion of such criteria is important to avoid misclassifying an ischemic CRVO as nonischemic. We chose to include functional and morphologic parameters over the first year of follow-up while classifying a CRVO as ischemic or not. We did this to see whether baseline IsI values could not only help in classifying a CRVO as ischemic or not at the baseline visit but also predict whether a patient was likely to convert to an ischemic CRVO during the first year of follow-up. The 6 eyes in this study which did not meet ischemic CRVO criteria at the baseline visit but did subsequently all had an IsI $>35\%$.

Presenting and final vision were significantly worse for the group with an IsI $\geq 35\%$. This is despite a similar number of anti-VEGF injections during the first year of follow-up and not significantly different baseline and final CST. Additionally, eyes with an IsI $\geq 35\%$ were over 6 times as likely to have a final acuity of 20/200 or worse. The observed difference in vision is likely in part related to a greater prevalence of ischemic maculopathy as evidenced by a significantly greater prevalence of foveal avascular zone enlargement in eyes with an IsI $\geq 35\%$. Evaluation for foveal avascular zone enlargement at baseline is not, however, adequate in determining visual prognosis. Campochiaro et al noted that reperfusion of areas of retinal nonperfusion occurred in 6% to 8% of eyes receiving ranibizumab.[15] Whether anti-VEGF therapy reduces the degree of retinal nonperfusion in retinal vascular disease as seen on UWFFA is being evaluated in prospective studies such as the ANDROID (ClinicalTrials.gov identifier: NCT01724554) and RECOVER (ClinicalTrials.gov identifier: NCT02863354) trails. Unpublished data from the ANDROID study suggest that aflibercept may reverse capillary nonperfusion, but the effects may revert with cessation of therapy.[16]

This study has several important limitations inherent to any single-center retrospective analysis. Although the intergrader agreement for IsI calculations was excellent, image enhancement in photoediting software was used which is not done in clinical practice. Although UWFFA captures a great deal more of retinal periphery than was previously possible, there is great variation in the degree of the periphery imaged and quality of the images based on patient and technician variability. It is important to note that although the IsI has been validated in previous studies, it is not an accurate reflection of the percentage of nonperfused retina. As UWF images map a 3-dimensional structure onto a 2-dimensional surface, there is significant warpage of peripheral pixels. However, a study by Tan et al compared IsI values with precise areas of nonperfusion (mm^2) on UWFFA and found excellent correlation ($r = 0.978$, $P < 0.001$).[17] In our study, we classified patients with very poor vision and an APD as having an ischemic CRVO.

Although most of the patients included in this fashion likely had an ischemic CRVO, it is possible that some had a nonischemic CRVO. Importantly, as we did not get follow-up UWFFA on our study patients, we are unable to provide additional angiographic data on the 2 patients who were classified as ischemic CRVO but had an IsI <35%. The baseline IsI on these patients was 6.2% and 8.7%.

Our data support the idea that a baseline IsI of ≥35% may be an important angiographic criterion to classify a CRVO as ischemic during the first year of follow-up. Classifying a CRVO as ischemic based on an IsI ≥35% was sensitive (90%) and specific (92.5%) and had a good positive predictive value (86%) and an excellent negative predictive value (95%). What remains to be seen is whether we can alter the clinical course of such patients. As results become available from clinical trials evaluating changes in capillary nonperfusion in response to anti-VEGF therapy, there may be data to support continued anti-VEGF therapy in eyes even after cystoid macular edema resolves. Early panretinal photocoagulation did not show benefit in eyes with an ischemic CRVO in the Central Vein Occlusion Study[18] and a more recent study did not show an improvement in vision or treatment burden after targeted panretinal photocoagulation to areas of nonperfusion in CRVO although follow-up time was brief.[19] To fully answer this question, we need better long-term data in eyes meeting updated criteria for an ischemic CRVO based on UWFFA findings.

Key words: central retinal vein occlusion (CRVO), fluorescein angiography, ischemic index.

References

1. Hayreh SS. Classification of central retinal vein occlusion. Ophthalmology 1983;90:458–474.
2. Hayreh SS, Rojas P, Podhajsky P, et al. Ocular neovascularization with retinal vascular occlusion-III. Incidence of ocular neovascularization with retinal vein occlusion. Ophthalmology 1983;90:488–506.
3. Hayreh SS, Zimmerman MB. Ocular neovascularization associated with central and hemicentral retinal vein occlusion. Retina 2012;32:1553–1565.
4. Natural history and clinical management of central retinal vein occlusion. The central vein occlusion study group. Arch Ophthalmol 1997;115:486–491.
5. Hayreh SS, Klugman MR, Beri M, et al. Differentiation of ischemic from non-ischemic central retinal vein occlusion during the early acute phase. Graefes Arch Clin Exp Ophthalmol 1990;228:201–217.
6. Nicholson BP, Nigam D, Miller D, et al. Comparison of wide-field fluorescein angiography and 9-field montage angiography in uveitis. Am J Ophthalmol 2014;157:673–677.
7. Prasad PS, Oliver SC, Coffee RE, et al. Ultra wide-field angiographic characteristics of branch retinal and hemicentral retinal vein occlusion. Ophthalmology 2010;117:780–784.
8. Singer M, Tan CS, Bell D, Sadda SR. Area of peripheral retinal nonperfusion and treatment response in branch and central retinal vein occlusion. Retina 2014;34:1736–1742.
9. Tsui I, Kaines A, Havunjian MA, et al. Ischemic index and neovascularization in central retinal vein occlusion. Retina 2011;31:105–110.
10. Wessel MM, Nair N, Aaker GD, et al. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. Br J Ophthalmol 2012;96:694–698.
11. Patel RD, Messner LV, Teitelbaum B, et al. Characterization of ischemic index using ultra-widefield fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. Am J Ophthalmol 2013;155:1038–1044.e2.
12. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010;117:1124–1133.e1.
13. Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor trap-eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. Ophthalmology 2012;119:1024–1032.
14. Decroos FC, Todorich B, Alshareef R, et al. Neovascular events in eyes with central retinal vein occlusion undergoing serial bevacizumab or ranibizumab intravitreal injections: a retrospective review. J Ophthalmic Vis Res 2014;9:461–468.
15. Tan CS, Chew MC, van Hemert J, et al. Measuring the precise area of peripheral retinal non-perfusion using ultra-widefield imaging and its correlation with the ischaemic index. Br J Ophthalmol 2016;100:235–239.
16. Campochiaro PA, Bhisitkul RB, Shapiro H, Rubio RG. Vascular endothelial growth factor promotes progressive retinal nonperfusion in patients with retinal vein occlusion. Ophthalmology 2013;120:795–802.
17. Heier J. The Effect of Intravitreal Aflibercept on Capillary Non-Perfusion in Patients With Proliferative Retinopathy and/or Macular Edema Secondary to Proliferative Diabetic Retinopathy and Central Retinal Venous Occlusive Disease (ANDROID Study). Paris, France: Retina Society; 2015.
18. Spaide RF. Prospective study of peripheral panretinal photocoagulation of areas of nonperfusion in central retinal vein occlusion. Retina 2013;33:56–62.
19. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The central vein occlusion study group N report. Ophthalmology 1995;102:1434–1444.