TECHNIQUE OF LASER CHORIORETINAL ANASTOMOSIS CREATION IN CENTRAL RETINAL VEIN OCCLUSION AND SUCCESS RATE WITH A NEW PHOTOCOAGULATOR SYSTEM

IAN L. McALLISTER, MBBS, DM,* LYNNE A. SMITHIES, PhD,* VICTOR PREVIN, BEng†

Purpose: To evaluate the success rate of laser chorioretinal anastomosis (L-CRA) creation with a new laser photocoagulator system capable of 5 watts (W) power in patients with central retinal vein occlusion (CRVO).

Methods: Patients with a treatment-naive CRVO were enrolled as part of an ongoing trial combining L-CRAs with anti–vascular endothelial growth factor treatment.

Results: Thirty-three patients were treated with an L-CRA developing in 29 (88%). Mean power was 2.7 W and mean time for development was 1.8 months. Each patient had two potential sites created. Eighteen patients developed 2 L-CRAs and the remaining 11 patients, one each. Of the 66 potential sites, successful L-CRAs developed at 47 sites (71%). Additional Nd:YAG laser applications were used in 39% of sites. Mean follow-up was 23 months and no significant complications were seen.

Conclusion: An L-CRA as a means of permanently bypassing the obstruction to venous outflow in CRVO may become more relevant as not all patients respond well to intravitreal therapy. The limitation to this technique in the past has been lack of availability of a laser system with the power necessary to create the L-CRA. The success rate with the new system has improved to 88% representing a significant improvement over our original success rate of 33%.

RETINA 36:1971–1978, 2016

The management of central retinal vein occlusion (CRVO) has changed considerably over the last 5 years. We now have the ability to improve the visual outcome of most patients with this condition rather than being only able to offer observation and treatment for the devastating end-stage sequelae of anterior segment neovascularization if it occurs.[1] Treatment for this condition now involves a number of compounds including vascular endothelial growth factor (VEGF) inhibitors and steroids that are directly injected into the vitreous cavity, all of which have been investigated in large phase three trials.[2–8] The effectiveness of these compounds has confirmed that the major cause of visual reduction in the early stages of retinal vein occlusion is macular edema. The pathogenesis of this is probably multifactorial with raised venous hydrostatic pressure, upregulation of various cytokines, and inflammatory components all potentially playing a role.

An additional potential treatment investigated by us is to use a high-power density laser to create a connection or anastomosis between a retinal vein where because of the obstruction to venous outflow, the intraluminal pressure is high and an unobstructed normal pressure choroidal vein.[9–16] In the Central retinal Vein Bypass Study (CVBS), a laser chorioretinal anastomosis (L-CRA) was successfully created in up to 76.5% of eyes treated with a subsequent

From the *Centre for Ophthalmology and Visual Science, Lions Eye Institute, The University of Western Australia, Perth, Australia; and †Ellex Medical Lasers, Adelaide, Australia.

Presented at the Retina Society 2015 annual meeting Paris, France, October 9, 2015.

V. Previn is an employee of Ellex medical lasers. None of the other authors have any financial/conflicting interests to disclose.

Reprint requests: Ian L. McAllister, MBBS, DM, Centre for Ophthalmology and Visual Science, Lions Eye Institute, The University of Western Australia, Nedlands, WA 6009, Australia; e-mail: ianmcallister@lei.org.au

improvement in vision.[15] This technique can address the component of the CRVO associated macular edema, which is caused by the elevated central venous pressure (CVP). This study used a purpose-built laser (HGM K3; Salt Lake City, UT) capable of up to 6 watts (W) of power. This laser however is no longer available, and as high-power densities are required to create the anastomosis, the lack of an appropriately powered laser has been a significant barrier to widespread uptake of this technique. We have previously investigated the efficacy of a newly developed prototype solid-state laser to deliver up to 5 W of power at 532 nm in an animal model[17] subsequently released to the market as the Integre Plus (Ellex, Adelaide, Australia). This laser has been shown to be capable of rupturing the retinal vein and Bruch membrane at lower power levels than previous laser systems. As previously demonstrated, these are the barriers that need to be breached to create an anastomosis.[10–12]

This article presents the technique and preliminary success rates of L-CRA creation with a purpose designed laser system in a current ongoing trial of a combination approach to the treatment of CRVO using both the L-CRA and intravitreal ranibizumab compared with ranibizumab alone.

Patients and Methods

The trial has enrolled patients with a recent treatment-naive CRVO with visual acuities between 20/320 and 20/40 (73–24 Early Treatment Diabetic Retinopathy Study letters). Eyes with visual impairment due to macular edema (mean central foveal thickness greater or equal to 250 microns) involving the centre of the fovea due to CRVO with a duration of less than 9 months before the baseline visit were randomized 1:1 into the ranibizumab treatment group (Group 1) or the combination group of L-CRA and ranibizumab (Group 2). The primary objective was to compare and establish whether there is a significant difference in the number of ranibizumab injections according to the pro re nata retreatment protocol in the observational period from 6 to 24 months in patients with visual impairment due to macular edema secondary to CRVO treated with either a combination of ranibizumab and L-CRA or ranibizumab with a sham L-CRA. A reduction in the number of ranibizumab injections required in Group 2, and improved stability of vision may reflect the fact that this combined treatment addresses all components causing macular edema in CRVO unlike anti-VEGF therapy in isolation. This trial is ongoing, and this report is on the success rates of L-CRA creation in the first 33 patients treated with this technique.

The study adhered to the tenets of the Declaration of Helsinki, and the protocol was approved by the institutional review board and health research ethics committee at the Sir Charles Gardiner hospital and the University of Western Australia. All patients provided written informed consent before participation in the trial. The trial is registered at the Australian New Zealand Clinical Trials Registry (ACTRN12612000004864).

Laser

The laser used in this study was the Integre Plus (Ellex), a solid-state laser photocoagulator equipped with a special mode that can be activated to deliver power of up to 5 W at 532 nm, together with custom temporal and spatial settings that make the laser significantly different from the HGM K3 laser used in the original studies, both in terms of its capacity and delivery system. This laser is now commercially available.

First, comparing the spatial profile at the 50-micron spot size setting, the laser delivered a smaller more confined 54-micron (μm) diameter laser spot, whereas the HGM K3 laser delivered a 64-μm spot (as measured by a Coherent Beamview Analyser LaserCam IIID). The interaction between the laser and the tissue is heavily dependent on the energy density of the incident beam. The energy density is inversely proportional to square of the spot diameter. Accordingly, the Ellex laser can achieve a 29% higher energy density, compared with the HGM K3 laser at the same power setting. As a result, with the Ellex laser, the same rupture effect on the retinal vein wall or Bruch membrane can be achieved with only 71% ($54^2/64^2$ = 0.71) of the power required by the HGM K3 laser.[14–17] The lower power delivered to the patient's eye combined with the more focused beam may potentially reduce the lateral spread of laser energy in the choroid and limit retinal pigment epithelial and choroidal damage.[11]

Second, the Ellex laser was optimized with structured temporal pulse shaping (STemPS) to deliver a temporal waveform with a sharp leading edge that promotes the conditions required for chorioretinal anastomosis through laser thermomechanical rupture of Bruch membrane and the vein wall. The initial high peak power induces a prompt temperature rise at the treatment site for localized evaporation of tissue. The trailing decline in power serves to compensate for thermal heat loss maintaining the central temperature (Figure 1). In combination with the smaller focused laser spot at the treatment target, this scheme may

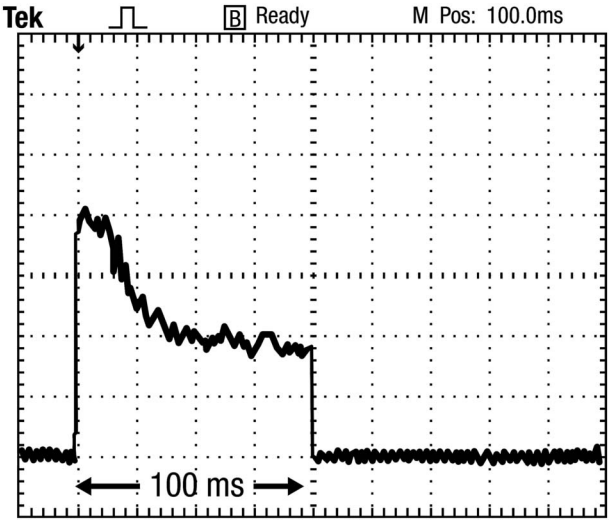

Fig. 1. Oscilloscope screen image showing typical temporal laser power profile delivered from the Ellex Integre plus laser at 5-watt peak power with 100-millisecond pulse width set to STemPS mode.

reduce collateral thermal damage to the surrounding choroidal vasculature from thermal diffusion.[11,17]

Third, the Ellex laser emits at the 532-nm wavelength, whereas the HGM K3 laser was at 514 nm. The hemoglobin absorption at 532 nm is approximately 50% higher than at 514 nm, and this may result in more efficient rupturing of the retinal vein and Bruch membrane.[18] As a result, less power may therefore be required.

Technique

Either a nasal vein or a second-order temporal retinal vein close to its junction with the major quadrantic vein is a preferred site. Two sites are chosen, above and below the horizontal midline, to maximize the chances of an L-CRV developing and also because 20% of eyes have a dual or hemicentral arrangement of retinal veins passing through the lamina cribrosa, which may not be easily identified with a swollen hemorrhagic optic disk as often seen with an acute CRVO.[19] The distance from the optic disk should be from two to five disk diameters. If possible, the chosen site should not exhibit a prominent arterial branch crossing over the venous segment between it and the optic disk. This can be difficult to determine when there is significant hemorrhagic retinopathy, but compression by the arteriole can lead to narrowing of the segment of the vein between it and the optic disk, thereby leaving the L-CRA to drain effectively only a segment of the retinal circulation (Figure 2C). The chosen site for the first laser application should be just adjacent to and touching the retinal vein wall with the aim of this laser application rupturing the underlying Bruch membrane. The power of the laser was set between 2.5 and 3.5 W depending on the degree of cataract, media opacity, and retinal edema. The spot size is set to 50 μm, the duration to 0.1 seconds, and the laser is applied through the central portion of a 3-mirror contact lens under topical anesthesia. The first laser application usually causes some heat constrictions of the adjacent vein and often, but, not always, a small bubble or cavitation is seen in the choroid. It is necessary to allow time to elapse for the vein to reopen before placing a second laser spot over the side wall of the vein with the aim of rupturing it on the same side as the original spot aimed at Bruch membrane. In approximately 60% of cases, this will rupture the vein wall, producing a small amount of visible hemorrhage, although time must be allowed to elapse while observing the laser spots for the vein to reopen. This may take several minutes. The hemorrhage from the retinal vein is usually minor and is easily controlled by placing pressure on the eye to the stage where the central retinal artery is closed for up to a minute (Figure 2, A and B). If there is no visible hemorrhage from the retinal vein once the vein reopens then a neodymium: yttrium aluminum garnet (Nd:YAG) laser is used with powers of 2 to 4 milli-Joules (mJ) to clip the side wall of the vein on the same side as the original 532-nm laser application. The aim is to breach both Bruch membrane and the side wall of the vein (Figure 2, A and B). This procedure should not be performed on patients who are significantly anticoagulated.

If an anastomosis is to develop, it will take between 2 and 6 weeks to become apparent with vascular remodeling seen on biomicroscopy and flow patterns that can be identified both by fluorescein and indocyanine green angiography (Figure 3). Anti-VEGF agents should not be given for at least 1 month after the anastomosis attempt as there is circumstantial evidence that development of the L-CRA is VEGF dependant.[16] Follow-up at monthly intervals is important, and at each visit, the anastomosis site should be observed for any evidence of choroidal neovascularization or closure of the segment of the vein distal to the site. If this occurs, the segment that the vein drains distal to the anastomosis site can be treated with sectorial laser photocoagulation making sure to leave at least a disk diameter untreated from the site to avoid damage to choroidal vasculature that may be involved in the developing anastomosis (Figure 3). Retinochoroidal neovascularization from the anastomosis site is very sensitive to intravitreal anti-VEGF agents and is now easily controlled. Macular edema can be treated with anti-VEGF agents commencing 1 month after the

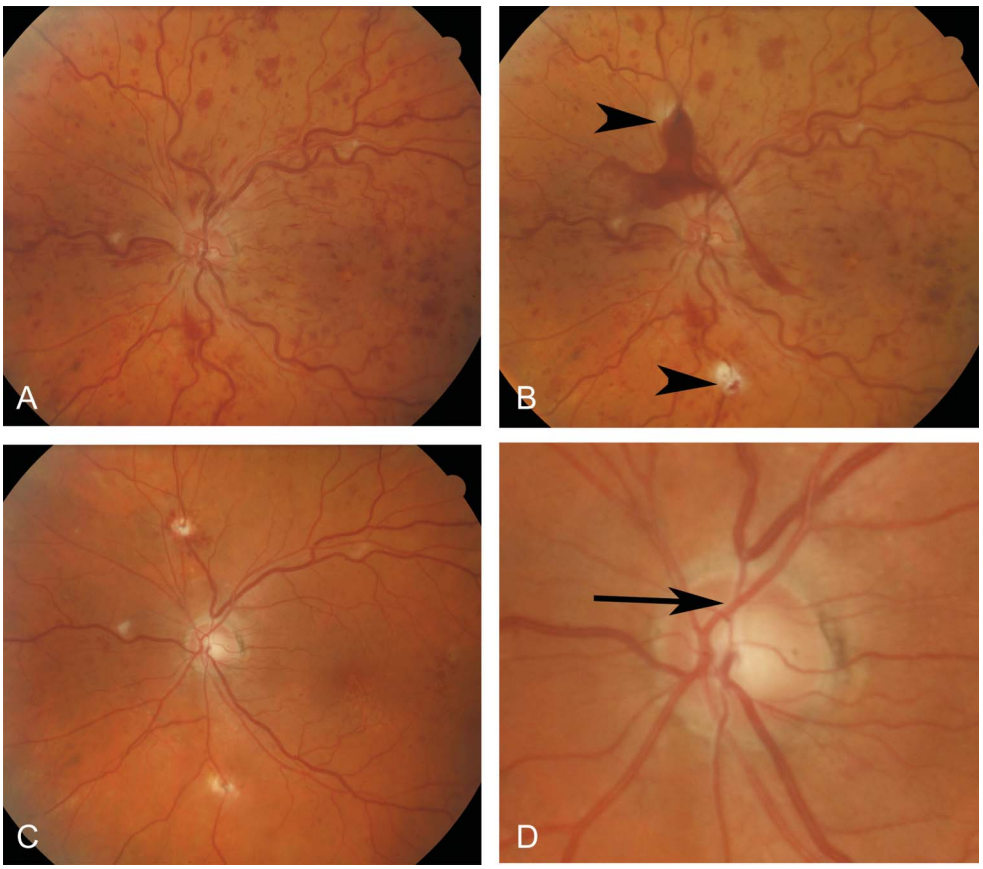

Fig. 2. A. Central retinal vein occlusion (CRVO) before laser chorioretinal anastomosis (L-CRA) creation. **B.** Immediately after L-CRA creation. Two sites are seen above and below the optic disk (arrow heads). The superior one has a small amount of vitreous hemorrhage which has been controlled by pressure on the eye by the 3-mirror contact lens. The inferior one has a small hemorrhage over the laser site, which is more typical of what is seen after the procedure. **C.** Four months after the laser application. There is resolution of the CRVO with L-CRAs seen above and below the optic disk. The superior one has an arteriole crossing over the segment of the vein leading to the optic disk, which has narrowed leaving this L-CRA to drain effectively only the superior retinal circulation. **D.** Magnified image of the superior temporal artery on the optic disk (arrow) crossing over and compressing the venous segment restricting drainage to the superior L-CRA.

laser attempt while waiting for the anastomosis to fully develop and become hemodynamically significant.

Results

Thirty-three patients (24 males and 9 females) with ages ranging from 46 to 86 years (mean 69 years) underwent the L-CRA procedure. Twenty-nine patients were in Group 2 of the trial and the remaining 4 while assessed as suitable for entry were not able to meet the strict follow-up of the protocol and were not enrolled. The 33 patients represent the first consecutive group of treated with the Ellex laser. One eye only in each patient was treated, with 14 right eyes and 19 left eyes. The duration of the CRVO ranged from 2 to 24 weeks (mean 7.2 weeks). Presenting visual acuity ranged from 26 to 73 letters (20/320–20/40) (mean 56 letters [20/80]). Of the 33 patients treated with the L-CRA, 29 developed at least 1 successful anastomosis (88%). Each patient had two potential sites created with one in the superior hemisphere and the remaining one in the inferior hemisphere. Eighteen patients developed 2 L-CRAs and the remaining 11 patients 1 L-CRA each. Of the 66 potential sites created in the 33 eyes, successful L-CRAs developed at 47 sites (71%). Twenty-three of these were in the superior hemisphere and 24 in the inferior. The power of the Ellex laser used at each site varied from 2.0 to 3.6 W (mean 2.7 W). Of the 66 sites attempted, the laser was successful in rupturing the side wall of the vein in 40 (61%). The remaining 26 sites (39%) had subsequent Nd:YAG laser applications to the side wall of the vein with powers ranging from 2.4 to 2.8 mJ. Evidence of rupture of the vein wall was seen at 64 of the 66 sites. Time for the development of the L-CRA varied from 1 to 6 months (mean 1.8). Complications at the 66 sites included closure of the distal segment of the vein at 8 sites (12%), resulting in wedge-shaped areas of peripheral retinal capillary nonperfusion, which were promptly treated with segmental pan retinal laser to reduce the incidence of retinal neovascularization. Small new vessel development was seen at 11 sites (17%), 5 of which regressed spontaneously and the remaining 6 were treated with sectorial laser peripheral to the L-CRA site. Two patients developed minor macular traction from avascular fibrous tissue proliferation treated with a vitrectomy. No patient developed significant retinochoroidal neovascularization requiring

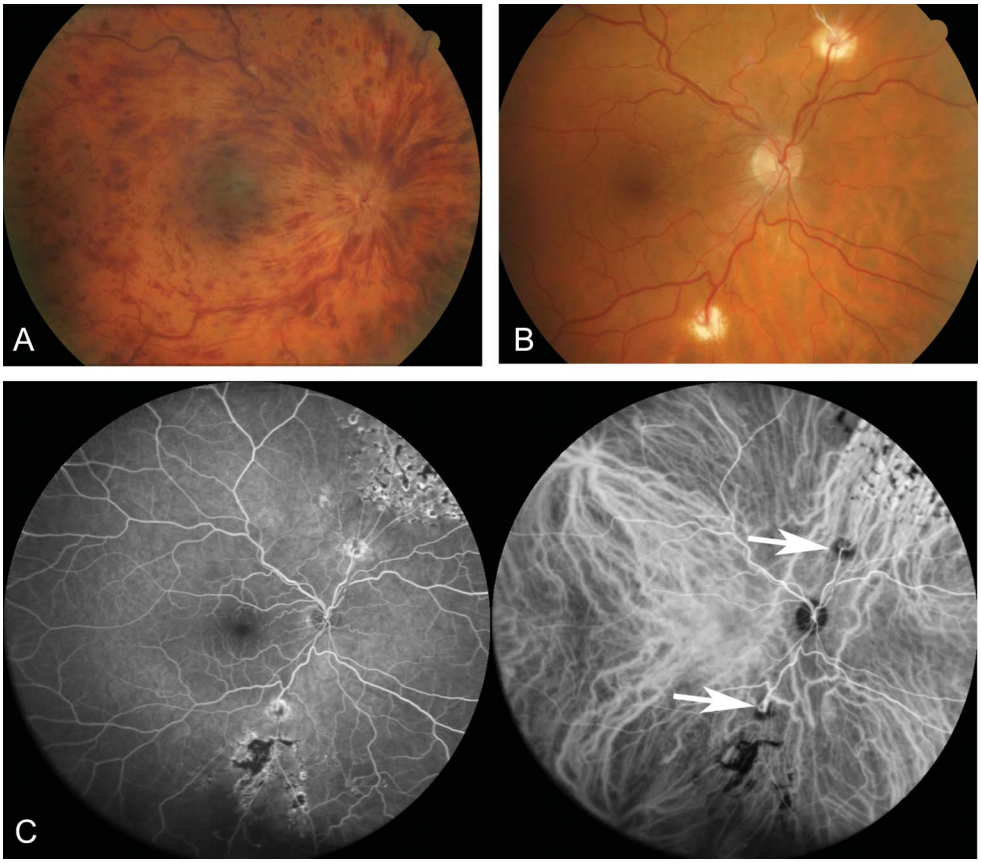

Fig. 3. A. Central retinal vein occlusion before laser chorioretinal anastomosis (L-CRA) creation. **B.** Seven months later with well developed L-CRAs above and below the optic disk. Both had closure of the distal segment of the retinal vein, which was treated with sectorial laser photocoagulation. The superior one also has a small neovascular frond, which has regressed without sequelae. **C.** Combined fluorescein and indocyanine green angiography showing the retinal veins draining into large choroidal veins (white arrows).

vitrectomy surgery. Follow-up varied from 6 to 38 months (mean 23 months).

Discussion

Success rates for the creation of an L-CRA have improved significantly from those achieved in our initial pilot study into this treatment technique in patients suffering from a nonischemic CRVO. In this original study, a conventional argon green laser with power levels ranging from 1.5 to 2.5 W was used, which produced a success rate of 33% in the patients treated.[13] Subsequent further experimental work on the need for appropriate laser power densities to puncture Bruch membrane and the side wall of the retinal vein led to further improvements in success rates.[10–12] Improvements in power (up to 4 W) in a conventional argon tube laser, with the additional use of a Nd:YAG laser to breach the side wall of the vein if not achieved with the initial laser application, improved the success rate to 53% of patients treated.[14] The CVBS was a randomized Phase 3 multicenter study comparing treatment with an L-CRA to the conventional treatment of the time in patients with a CRVO. In this study, a purpose-built HGM K3 laser capable of up to 6 W, again with the additional use of a Nd:YAG laser when necessary, was used. In this study, power levels of between 3.5 W and 6 W were used, depending on the degree of media opacity and retinal edema. These were graded and powers adjusted on a sliding scale. A success rate of L-CRA creation occurred in 76.5% of patients although three attempts were allowable under the study protocol each with 2 sites.[15] Of the total of 52 L-CRAs created in 42 patients in the CVBS, 43 (82.7%) were created in the first attempt, 8 (15.4%) were created in the second attempt, and 1 only was created in the third attempt (1.9%).[15,16]

The success rate of L-CRA creation in 88% of patients with the use of the Ellex laser with only 1 attempt allowable represents a considerable improvement compared with the results of our previous studies. This improvement reflects our better understanding of the endpoints required to achieve an anastomosis after the laser application, together with the use of a more refined purpose-built laser. The use of this laser was only considered after it had been investigated in an animal model to determine whether the power levels reached were capable of achieving the anatomical endpoints sought, namely, a reliable

rupture of both Bruch membrane and the side wall of the retinal vein.[17] The mean power used in this study was 2.7 W, which should be capable of reliably creating a defect in the underlying Bruch membrane. In the animal study, a localized rupture of Bruch membrane was seen at all power levels above 1 W; however, these were all were young animals with clear ocular media unlike most patients with CRVO where higher powers would be needed. The average level of laser power used in this study of 2.7 W successfully ruptured the side wall of the retinal vein in 67.5%, which is very similar to the results achieved in the animal study.[17]

Treatment of CRVO in the future may require a more comprehensive approach addressing all components, which cause the visual reduction seen in this condition. The current standard of treatment of CRVO is the use of intravitreal agents, which through a variety of mechanisms address the breakdown of the blood retinal barrier that contribute to the macular edema. The success of these intravitreal compounds is due to their ability to modify the effect of the predominant cytokine involved, VEGF-A, which is known to be significantly upregulated in CRVO and also to increase vascular permeability.[20,21]

Although these agents have all shown varying degrees of effectiveness in resolving the macular edema in the short term, with commensurate improvements in visual acuity, many have recurrences of the edema once the effect of the agent has worn off, thereby requiring repeated injections for an as of yet undetermined period of time which can be years. In addition, longer-term studies have shown that the initial visual acuity gains are not sustained with mean visual acuity decreasing in the second and subsequent years.[22–24]

These intravitreal agents are effective in addressing the VEGF-induced breakdown in the blood retina barrier, which is 1 component of the CRVO-induced macular edema; however, they fail to address the other major cause, which is the elevation of the CVP. This is caused by the blockage to retinal venous outflow, which in a closed vascular system such as the retinal circulation is transmitted to the smaller vessels and capillaries. This outflow obstruction can result in a significant elevation of the intravenous hydrostatic pressure with ophthalmodynamometric assessments indicating that the CVP in this condition can be up to 24 times of that found in an unobstructed central retinal vein.[25] We have previously shown that significant elevation of the CVP in CRVO is a major cause of poor visual outcomes and ischemic consequences.[26]

Although there is little debate that the clinical features of CRVO are caused by an obstruction to venous outflow, the exact site and the sequence of causative pathological events remain controversial. Given that we can now accept that the elevation in CVP that this obstruction causes is a significant factor in the visual outcomes that occur in this condition, a treatment directed to this component is required. The only options are to either relieve the obstruction or bypass it. Attempts have been made to relieve the obstruction in the central retinal vein but currently none of these have been proven to offer any benefit to final outcomes. The L-CRA is a procedure that is directed to causal pathology in CRVO and requires a high-power laser to create the anastomotic connection between the obstructed retinal venous circulation and a choroidal vein as a means of bypassing the obstruction to venous outflow in the central retinal vein.[16,17] This has been proven to be effective and to improve visual outcomes. It does, however, require a laser with higher power than is currently available, which has been a barrier to more widespread adoption of this technique. The original laser used in the CVBS is no longer available, and the Ellex laser produces power densities that are suitable and has the highest success rate of L-CRA creation that we have achieved thus so far.

Complications associated with the procedure are now easily managed. Our initial studies indicated that untreated areas of retinal ischemia were associated with a greater incidence of retinal neovascularization at the site of the L-CRA.[14] This observation led to the recommendation that any patients treated with this technique be carefully followed and if neovascularization did develop then such areas be identified by fluorescein angiography and promptly treated with laser photocoagulation. Similarly, any induced areas of retinal ischemia such as those seen if the segment of retinal vein distal to the L-CRA closes should also be prophylactically treated with segmental laser to reduce the risk of neovascular complications. This was performed at 8 of the 66 sites (12%). Small neovascular fronds were seen at 11 of the 66 sites (17%). At six sites, these regressed after segmental laser applied distal to the L-CRA site, and in the remaining five, regression occurred spontaneously. In this study, intravitreal ranibizumab was commenced 1 month after the L-CRA attempt, which may have induced regression. Spontaneous regression, perhaps, similar to a localized vascular steal phenomenon as the L-CRA developed, was seen in the CVBS, which was performed before the availability of intravitreal VEGF antagonists, which are now highly effective in controlling neovascular complications.[15,27] Careful and regular follow-up after the L-CRA procedure is still required to detect these developments should they occur and also to ensure treatment is commenced

before significant tractional changes develop. Vitrectomies were required in two patients (6%) to relieve early macular traction from avascular fibrous tissue proliferation. This complication has been documented previously and seems to be similar to the tissue seen in an epiretinal membrane.[14] The mechanism is uncertain but possibly related to the defect in the internal limiting membrane caused by the laser or initiated by neovascularization that regresses.

The role of the L-CRA in the overall management strategy for CRVO will be better defined by the current ongoing combinational study. Whether it should be reserved for patients with CRVOs who have a worse prognosis (poor presenting visual acuity, high CVP[26]) or those that fail to respond to a trial of anti-VEGF therapy remains to be determined. However, given the limitations of current treatment regimens and as this procedure is the only proven technique for addressing the elevated CVP that occurs in CRVO with its associated consequences for macular edema and retinal ischemia, the development of a laser system that is capable of reliably creating the L-CRA has been urgently needed.[26]

Key words: central retinal vein occlusion, laser chorioretinal anastomosis, laser photocoagulation.

References

1. 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.
2. Ip MS, Scott IU, VanVeldhuisen PC, et al; The SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. Arch Ophthalmol 2009;127:1101–1114.
3. Haller JA, Bandello F, Belfort R Jr, et al; for the OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 2010; 117:1134–1146.
4. Wroblewski JJ, Wells JA, Adamis AP, et al. Pegaptanib sodium for macular edema secondary to central retinal vein occlusion. Arch Ophthalmol 2009;127:374–380.
5. Brown DM, Campochiaro PA, Singh RP, et al; for the CRUISE Investigators. 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.
6. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. Ophthalmology 2011;118:2041–2049.
7. Brown DM, Heier JS, Clark WL, et al. Intravitreal aflibercept for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. Am J Ophthalmol 2013;155:429–437.
8. Holz FG, Roider J, Ogura Y, et al. VEGF trap-eye for macular edema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol 2013;97:278–284.
9. McAllister IL, Yu DY, Vijayasekaran S, et al. Induced chorioretinal venous anastomosis in experimental retinal branch vein occlusion. Br J Ophthalmol 1992;76:615–620.
10. Vijayasekaran S, Yu DY, McAllister IL, et al. Significance of Bruch's membrane in the creation of iatrogenic chorioretinal venous anastomosis. Curr Eye Res 1994;13:29–33.
11. Vijayasekaran S, Yu DY, McAllister IL, et al. Optimal conditions required for the creation of an iatrogenic chorioretinal venous anastomosis in the dog using argon green laser photocoagulation. Curr Eye Res 1995;14:63–70.
12. McAllister IL, Vijayasekaran S, Yu DY, Constable IJ. Chorioretinal venous anastomoses: effect of different laser methods and energy in human eyes without vein occlusion. Graefes Arch Clin Exp Ophthalmol 1998;236:174–181.
13. McAllister IL, Constable IJ. Laser-induced chorioretinal venous anastomosis for treatment of nonischemic central retinal vein occlusion. Arch Ophthalmol 1995;113:456–462.
14. McAllister IL, Douglas JP, Constable IJ, Yu DY. Laser-induced chorioretinal venous anastomosis for non-ischemic central retinal vein occlusion: evaluation of the complications and their risk factors. Am J Ophthalmol 1998;126: 219–229.
15. McAllister IL, Gillies ME, Smithies LA, et al. The central retinal vein bypass study: a trial of laser-induced chorioretinal venous anastomosis for central retinal vein occlusion. Ophthalmology 2010;117:954–965.
16. McAllister IL, Gillies ME, Smithies LA, et al. Factors promoting success and influencing complications in laser-induced central vein bypass. Ophthalmology 2012;119:2579–2586.
17. McAllister IL, Vijayasekaran S, Xia W, Yu DY. Evaluation of the ability of a photocoagulator to rupture the retinal vein and Bruch's membrane for potential vein bypass in retinal vein occlusion. Ophthalmic Surg Lasers Imaging Retina 2013;44: 268–273.
18. Friebel M, Roggan A, Müller G, Meinke M. Determination of optical properties of human blood in the spectral range 250 to 1100 nm using Monte Carlo simulations with hematocrit-dependent effective scattering phase functions. J Biomed Opt 2006;11:034021.
19. Chopdar A. Dual trunk central retinal vein incidence in clinical practice. Arch Ophthalmol 1984;102:85–87.
20. Pe'er J, Folberg R, Itin A, et al. Vascular endothelial growth factor upregulation in human central retinal vein occlusion. Ophthalmology 1998;105:412–416.
21. Ozaki H, Hayashi H, Vinores SA, et al. Intravitreal sustained release of VEGF causes retinal neovascularisation in rabbits and breakdown of the blood-retinal barrier in rabbits and primates. Exp Eye Res 1997;64:505–517.
22. Heier JS, Campochiaro PA, Yau L, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology 2012;119: 802–809.
23. Campochiaro PA, Sophie R, Pearlman J, et al. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: the RETAIN study. Ophthalmology 2014;121: 209–219.
24. Heier JS, Clark WL, Boyer DS, et al. Intravitreal Afibercept injection for macular edema due to central retinal vein

occlusion: two-year results from the COPERNICUS study. Ophthalmology 2014;121:1414–1420.
25. Jonas JB. Ophthalmodynamometric assessment of the central retinal vein collapse pressure in eyes with retinal stasis or occlusion. Graefes Arch Clin Exp Ophthalmol 2003;241:367–370.
26. McAllister IL, Tan MH, Smithies LA, Wong WL. The effect of central retinal venous pressure in patients with central retinal vein occlusion and a high mean area of nonperfusion. Ophthalmology 2014;121:2228–2236.
27. Fong CS, Barry C, McAllister IL. Intravitreal bevacizumab (Avastin) as a treatment of the neovascular complications of laser-induced chorioretinal anastomosis for nonischaemic central retinal vein occlusion. Clin Exp Ophthalmol 2009;37: 485–489.