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Chorioretinal Anastomosis for Central Retinal Vein Occlusion: A Review of Its Development, Technique, Complications, and Role in Management

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Abstract: Treatments for central retinal vein occlusion (CRVO) have improved dramatically with the advent of intravitreal agents aimed at blocking the effects of the dominant hypoxia-induced upreglulated cytokine, which is vascular endothelial growth factor (VEGF). This cytokine breaks down the capillary endothelial barriers and is a major component of the macular edema in this condition. These treatments although impressive only address some of the sequelae of CRVO and have no effect on the underlying cause which is an obstruction to venous outflow leading to retinal blood flow stagnation and an elevation of the retinal central venous pressure (CVP). The creation of a laser-induced chorioretinal anastomosis (L-CRA) between the obstructed high pressure retinal venous circulation and the unobstructed low pressure choroidal venous circulation is a means addressing the causal pathology. The L-CRA will help lower the elevated CVP, which has been up until now an unaddressed component of the macular edema in this condition. This article reviews the preclinical and clinical development of the L-CRA and the results of the studies into its effect on the natural history of CRVO. It now can be used in combination with existing anti-VEGF treatments with the intravitreal agents addressing the component of the CRVO-induced macular edema due to the cytokine dysregulation, and the L-CRA addressing the component due to the elevated CVP and retinal venous stagnation. Improvements in laser technology have led to higher success rates in L-CRA creation and potential complications are now minimized and better controlled. The combination of L-CRA with intravitreal anti-VEGF agents offers the potential of a permanent cure with a significant reduction in the burden of therapy and improved visual outcomes in this condition.

Key Words: central retinal vein occlusion, central venous pressure, laser induced chorio-retinal anastomosis

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Central retinal vein occlusion (CRVO) remains a common cause of unilateral visual loss. Although it was originally described >150 years ago by Liebreich,[1] our understanding of its pathogenesis, our ability to modify the final visual outcome, and the availability of treatments to effectively intervene in the progression of this disorder are all relatively limited. Recently a number of randomized controlled clinical trials have reported on treatment options that provide significant improved visual acuity (VA) outcomes over the natural history.[2–6] The majority of these are directed at the sequelae of the obstruction in the retina to venous outflow,[2–5] with only 1, the laser chorioretinal anastomosis (L-CRA), directed at causal pathology.[6] This technique uses a high-power density laser to create an anastomotic connection between an obstructed retinal vein and an underlying choroidal vein as a means of permanently bypassing the obstruction to retinal venous outflow that occurs in this condition.

PREVALENCE OF CRVO

CRVO remains a relatively common cause of usually unilateral visual loss which can be significant justifying the pursuit of causal based therapies. Prevalence rates reported from population based studies range from 0.1% to 0.5% for predominantly the middle aged to older age groups.[7,8] Pooled data from individual population based studies have indicated that the prevalence for CRVO is 0.8 per 1000 (confidence interval 0.61–0.99).[9] Prevalence rates increase with age and do not differ by sex or race/ethnicity. It was estimated using these prevalence rates that 2.5 million adults were affected by CRVO worldwide using the 2008 world population.[9]

WHY CONSIDER AN L-CRA GIVEN THAT CURRENT TREATMENTS OFFER SIGNIFICANT VISUAL BENEFITS COMPARED WITH THE NATURAL HISTORY OF CRVO?

To answer this, we need to first review the natural history of CRVO, its pathogenesis, and the events triggered by this obstruction to venous outflow. We need to examine how these contribute to the retinal changes that occur in this condition and how these may be overcome.

Natural History

Outcomes for CRVO are poor if untreated in terms of ocular morbidity and visual loss. In the acute phase, visual reduction occurs due to macular hypoxia, cystoid macular edema (CMO), and intraretinal hemorrhage. Ultimately, Although some normalization of the retinal venous circulation may occur, there is for most a variable degree of long-term visual impairment. There is also the risk of both anterior segment, and more rarely posterior

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segment neovascularization which increases with the degree of retinal ischemia.[10–13] By the end of the 3-year CRVO study (CVOS), 34% of initially nonischemic eyes had converted to the ischemic category.[14] Anterior segment neovascularization developed in 16% of patients overall, and was seen in 10% of patients classified as initially nonischemic. Similar rates of conversion were seen in the control group of the central vein bypass study (CVBS) with 20.8% of eyes initially nonischemic converting to the ischemic category during the 18-month follow-up.[6]

A deterioration in VA over time has been reported in most studies of CRVO with the decrease being most pronounced in the ischemic group.[10] A meta-analysis of studies in which the change in VA could be calculated using LogMAR units indicated a pooled mean decrease in VA of 10 letters from baseline to 6 months and 3 letters from baseline to ≥12 months for nonischemic CRVO. For ischemic CRVO, the pooled mean decrease was 15 letters from baseline to 6 months and 35 letters from baseline to ≥12 months.[10] The CVOS found that final VA outcomes were highly influenced by VA at presentation and the degree of retinal ischemia.[12,14] Sixty-five percent of patients presenting with initially good VA (20/40) or better maintained this level of VA. For those in the intermediate group of presentation VA (20/50–20/200), VA improved to 20/50 for 19%, 44% stayed in the same range, and 37% deteriorated to <20/200. For those with initial poor VA (<20/200) there was an 80% chance of having a VA of <20/200 at the conclusion of the study. The control group of the CVBS study, which had VA entry criteria similar to the CVOS intermediate group, showed a very similar final VA result at the end of the 18-month follow-up.[6] These visual outcomes are influenced by the degree of ischemia in the macular capillary vasculature and the amount and persistence of CMO. The persistence of CMO can be significant as natural history studies of CRVO have shown, the median time to macular edema resolution is between 23 and 29 months.[15]

PATHOGENESIS

This remains incompletely understood and controversial. The obstruction to central retinal venous outflow is thought to occur in the region of, and just posterior to, the lamina cribrosa. Multiple factors are likely to be involved including a combination of local anatomical susceptibility, vessel wall changes, hemorrheologic and thrombotic tendencies. The hypothesis that a CRVO is due to a thrombus located in the central retinal vein (CRV), in the region of or just posterior to the lamina cribrosa, is based on anatomic features of the lamina cribrosa and also on an autopsy study of eyes with longstanding CRVO where evidence of thrombosis was found in the region of the lamina cribrosa.[16]

The CRV in the region of the lamina cribrosa has distinct anatomical arrangements which may make it prone to obstruction. The central retinal artery shares a common adventitial sheath with the CRV and compression of the vein by the more rigid arterial wall, especially in those with arteriosclerotic vascular disease may occur. Post mortem studies have demonstrated a natural constriction in the CRVO in this region in healthy eyes and more pronounced changes are seen with increasing age.[17] High blood velocities in the CRV at this site have been demonstrated, also suggesting the presence of a constriction.[18] These changes could then lead to greater shear stresses causing endothelial cell damage, which in turn could lead to endothelial cell proliferation and possible thrombus formation. Stress related changes are seen the venous endothelial cells in the region of the posterior lamina cribrosa supporting the theory that this is an area of hemodynamic stress.[19]

The above hypothesis assumes that the degree of obstruction to venous outflow in the region of the lamina cribrosa is variable and there is either a complete or incomplete occlusion of the CRV producing the variation in the clinical picture. Other investigators believe the variation in the clinical picture stems from the location of the blockage in the CRV.[16,17] Their hypothesis is that an occlusion of the CRVO in the lamina cribrosa region will produce a more complete obstruction to CRV outflow and hence a more severe or ischemic type clinical picture, whereas an occlusion further posterior to the lamina cribrosa will produce a less severe or nonischemic clinical condition. This is due to the fact that an occlusion posterior to the lamina cribrosa will allow some venous outflow via venous tributaries that occur in the CRV in the retrocribrosal region, which can form anastomoses with surrounding veins.

For CRVO, in regard to the nature and site of the obstruction to retinal venous outflow, which occurs in this situation, currently we have no definitive evidence as to what comprises the occlusion and where exactly in the CRV it lies.[20,21] Initially it is possible that this is a thrombus which potentially may be reversible; however, it is likely that secondary effects such as endothelial cell proliferation will progress and contribute subsequently. Attempts have been made in several small uncontrolled trials to lyse the presumed thrombus by direct injection of a thrombolytic into a retina vein with variable results and some risk of complications.[22,23] This would appear to be a simplistic approach as any thrombus that may be present would be the penultimate event in a series of pathological changes that have occurred in and around the CRV. Attempting to lyse this, although it may be initially successful, would do nothing to the underlying changes which led up to this obstruction occurring and the thrombosis would then be likely to reoccur. It would appear, if the causal pathology in CRVO is to be addressed, the option of directly reversing the obstruction in the CRV is not viable. If this is the case, then the only other option is to bypass it.

WHY IS IT NECESSARY TO ADDRESS THE CAUSAL PATHOLOGY GIVEN THE IMPRESSIVE RESULTS WITH CURRENT TREATMENTS?

To answer this, we need to consider the changes that occur in the retinal vasculature in a CRVO. The effectiveness of vascular endothelial growth factor (VEGF) blockade with frequent intravitreal injections in CRVO resulting in rapid improvements seen in both best-corrected visual acuity (BCVA) and central subfield thickness in the major randomized controlled trials that have investigated their use has confirmed that macular edema secondary to the upregulation of this cytokine is a predominate cause of the visual reduction seen in the early stages of this condition.[24,5] These treatments, although impressive in the short term, have no effect on the underlying pathology, which is an obstruction to venous outflow thought to occur within the intraneural portion of the CRV. This obstruction results in a reduction of retinal blood flow, leading to an upregulation of hypoxic induced cytokines, predominantly VEGF-A,[25,26] but also elevates the central venous pressure (CVP) which can be up to 24 times that of normal.[27] The

pathogenesis of macular edema in CRVO is multifactorial, with both the upregulation of VEGF and the elevated CVP having contributory effects. Although blockade of the upregulated VEGF is effective in the short term, both of these components need to be addressed to fully treat this condition in the longer term to achieve maximal BCVA and stability of vision. The intravitreal half-life of a 0.5-mg injection of ranibizumab is estimated to be 7.19 days and although this does dry out the macula, as seen by the larger studies, its effect soon wears off.[28] Elevated intraretinal VEGF levels downregulate the capillary endothelial barriers proteins and as the effect of the VEGF blockade wears off, these may leak more and this is likely to be exacerbated by the elevated CVP.[26,29]

Persistently elevated CVP in CRVO is associated with worse visual outcomes, greater degrees of retinal ischemia, and a higher incidence of anterior segment neovascularization.[30,31] Optical coherence tomography angiography advances have indicated that the deep capillary macular plexus, which has a lower perfusion pressure than the superficial plexus and drains predominantly into the retinal venous system may be more susceptible to stagnation and hypoxic damage from raised CVP.[32] It therefore is possible that persistently elevated CVP will through backpressure via the deep capillary macular plexus increase the risk of progressive hypoxic macular damage and recurrent edema.

Longer-term studies of intravitreal VEGF suppression in CRVO have shown that the initial gains achieved in the first year were not maintained over a subsequent year of treatment. In these studies, a BCVA loss of 4.3 to 4.9 letters from the levels achieved at the 6-month time-point was seen at the end of the second year with most patients still requiring ongoing intravitreal therapy.[33,34] Possible reasons include the treatment intervals being too long in the second year or patient fatigue with the burden of therapy and subsequent nonattendance. The results from "real world" type studies where recurrent injections are required for VEGF-mediated maculopathies would indicate that it is very difficult to achieve and maintain the same visual acuity gains that are seen in strict clinical trials in normal clinical practice where patients may not be willing to attend and receive the same intensity of treatment. Strict interval monitoring and an increased injection load can result in initial visual gains being maintained; however, patients with CRVO are more likely to experience reduced BCVA outcomes when the duration between follow-up visits is increased.[35,36] As natural history studies of CRVO have shown the median time to macular edema resolution is between 23 and 29 months, this does imply a considerable investment in time and resources in the treatment of this condition.[15]

LASER CHORIORETINAL ANASTOMOSIS

To achieve more sustainable results with less reliance on intravitreal therapy and ease the burden of treatment on the patient with a CRVO will require that the causative pathology in CRVO is more adequately addressed. Although anti-VEGF agents address the cytokine-mediated break-down in the blood ocular barrier with regular administration, they fail to address the CVP elevation that occurs in CRVO and the corresponding reduction in retinal blood flow. To correct this would require that the obstruction to venous outflow occurring in the central retinal vein be resolved. As a direct resolution of the obstruction in the central retinal vein currently appears to be impracticable, the only other option if we are to address the elevated CVP would be to bypass the site of the obstruction. This is achievable as an outpatient procedure with the L-CRA where an obstructed retinal vein is anastomosed with an unobstructed choroidal vein as a means of bypassing the central retinal vein (Fig. 1).[6,37–40]

The L-CRA procedure was initially investigated extensively in a laboratory model to prove the concept and answer the following[41–44]:

1. Was it possible to create an anastomosis between the retinal vein and a choroidal vein?
2. What anatomical barriers needed to be breached to establish an anastomosis?
3. What was the best modality to establish this—laser or surgery?
4. What power of laser, laser type, and wavelength, duration of laser burn, and spot size were required?
5. What potential complications could be expected from the procedure?
6. If an anastomosis could be created would it be of therapeutic benefit in a retinal vein occlusion?
7. How long would such an anastomosis last?
8. How long does it take for an anastomosis to develop?

Laser Development

The procedure has been refined over a number of years with the aim being to create a very localized puncture through both Bruch membrane and the chosen retinal vein to allow the L-CRA to develop without causing excessive damage to either the retina or the vasculature of the choroid, which if it occurred could impair the anastomotic connection. We have found the green laser [initially argon at 514 nm and later a frequency doubled neodymium: yttrium aluminum garnet (Nd-YAG) at 532 nm] to be most effective for creating the puncture through Bruch membrane. A small spot size of 50 μm with a duration of 0.1 second was used to limit retinal and choroidal vascular damage. Success rates have improved significantly with the acquisition of lasers capable of higher-power densities. The initial study used a conventional Coherent argon tube laser of the time (514 nm) and achieved a success rate of L-CRA creation of 33% for the patients with a CRVO with power levels of 1.5 to 2.5 watts (W).[37] From the initial laboratory studies we found that the anatomical barriers that the laser was required to breach to create the anastomotic connection between a retinal vein and a choroidal vein were both Bruch membrane and the side wall of the retinal vein. Sufficient Argon laser power is required to do this with a small spot size and a short duration to limit lateral spread of the laser energy within the choroid. The initial success rates were not sufficiently high to provide a reliably reproducible level of anastomosis creation, and despite the laser energies being used, this was not sufficient to reliably puncture both Bruch membrane and the side wall of the retinal vein, which were the anatomical barriers to the anastomosis development. By removing the software bar on the Coherent argon tube laser, we were able to increase the power output to 4.0 W which increased the success rate of the Bruch membrane puncture. Breaching the side wall of the retinal vein was less successful and in 34% of cases the Nd-YAG laser was used in addition to the argon laser to clip the side wall of the retinal vein just adjacent to the initial argon laser spot. Using this combination of higher argon laser power and the Nd-YAG where necessary we were able to increase the success rate to 54%.[38] After these improved success rates, a randomized trial, comparing the

FIGURE 1. CRVO at presentation (BCVA 6/24) and at 18 months (BCVA 6/6) after being treated with a combination of L-CRA and ranibizumab. A, L-CRA attempt showing laser burns on the retinal veins above and below the disc. Minute amounts of hemorrhage were seen from the vein. B, At 18 months showing L-CRAs above and below the disc (small arrows). The inferior one is draining only a localized segment with the vein between the L-CRA and the disc closed (large arrow). C, Fluorescein and (ICG) at 18 months with the L-CRAs seen (arrows). The ICG shows the large choroidal veins the anastomosis is draining into. D, OCT at presentation. E, OCT at 18 months. The patient has not required anti-VEGF for 10 months. BCVA indicates best-corrected visual acuity; CRVO, central retinal vein occlusion; ICG, indocyanine green angiogram; L-CRA, laser-induced chorioretinal anastomosis; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor.

outcomes of nonischemic CRVOs treated with an L-CRA compared with the conventional treatments of the time (pre anti-VEGF era) was performed. This study used a purpose built laser (HGM K3, Salt Lake City, UT) capable of up to 6 W of power. Power levels of 3.5 to 6.0 W were used with the Nd-YAG being used in 34%. The success rate of L-CRA creation was improved to 76.4%.[6] The HGM laser is no longer available as the company has ceased trading, 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. To address this, we in conjunction with Ellex, (Adelaide, Australia) developed and investigated the efficacy of newly developed prototype solid-state laser capable delivering up to 5 W of power at 532 nm in an animal model.[45] This laser has subsequently released to the market as the Ellex Integre Plus. This laser has shown to be capable of both rupturing the retinal vein and Bruch membrane at lower power levels than previous laser systems. The Ellex laser was able to achieve a 29% higher energy density, compared with the HGM K3 laser used in the original randomized trial at the same power setting due to a more refined beam profile which delivered a more confined 54 micron (μm) spot size with no blurring at the edges. The 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 via laser thermomechanical rupture of Bruch membrane and the vein wall.[40,45] These features allowed the success rate of the anastomosis to be improved to 88% with lower power levels of 2.0 to 3.6 W, although Nd-YAG usage was unchanged at 39%[40] (Table 1).

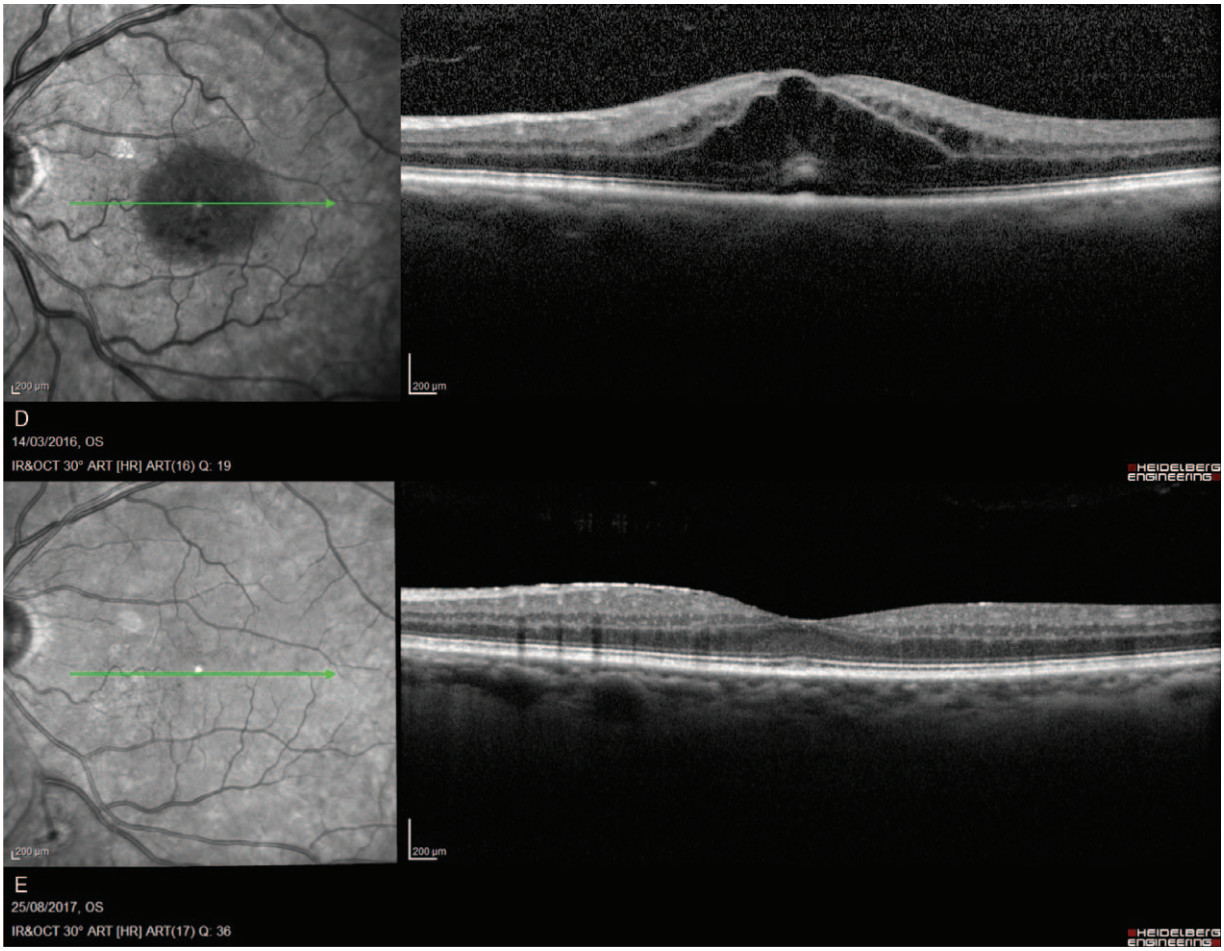

FIGURE 1. (Continued).

Other investigators have also attempted to treat CRVOs with the L-CRA technique.[46–50] These studies were all published before the improvements in laser technology that we developed to increase the likelihood of success and variable quoted success rates and complications were achieved. These studies were all generally small in number (6–61 eyes) and there was a wide range of reported success rates varying from 0 to 100%. It can be difficult in many instances to determine whether an attempt at creating an L-CRA has been successful especially if the overlying vein has been pulled down into a laser induced retinochoroidal scar. We now judge the success of L-CRA creation on: a combination of the features of the vein at the anastomosis site (alteration of the width of the vein with the proximal part being larger than the distal part, small venous loop at the anastomosis site); the characteristics of the early-phase fluorescein angiogram at the anastomosis site (tri-laminar flow in the proximal part leading into the L-CRA, retrograde flow in the proximal venous segment); the indocyanine green angiogram which will show a draining choroidal vessel if the L-CRA attempt has been successful.[6,37–40,54] It often takes 2 to 6 weeks before these signs develop, although in some cases may take longer. The study that quoted a success rate of 100% used a different technique aiming for an area adjacent to the chosen retinal vein with the aim of not directly puncturing it at the laser attempt.[50] They used a 50-µm spot with power levels of 0.6 to 1.5 W and duration of 0.5 or 1.0 seconds. Multiple applications (mean 7) and attempts (mean 1.8) were used. The authors quoted a success rate of 100% of eyes eventually developing an anastomosis with the only complications being localized preretinal fibrosis in at the L-CRA site in 26%.

Our experience with these laser parameters has not been the same, and indeed despite the quoted success rate of 100%, there has been no subsequent publications to confirm this by either these or subsequent authors. Our initial animal-based studies did indicate that longer duration laser applications did cause extensive

TABLE 1. Chronological Progression of Lasers Used to Create the L-CRA With Power Outputs and Success Rates in Anastomosis Creation

Laser	Wavelength, nm	Maximum Power, W	Power Used, W	Nd-YAG (%)	Success Rate (%)
Coherent tube laser (1995)	514	2.5	1.5–2.5	0	33
Coherent tube laser (bar removed) (1998)	514	4.0	0.6–4.0	34	54
HGM K3 (modified) (2010)	514	6.0	3.5–6.0	34	76.4
Ellex Integre Plus (2014)	532	5.0	2.0–3.6	39	88

% indicates percentage; L-CRA, laser chorio-retinal anastomosis; Nd-YAG, neodymium: yttrium aluminum garnet; nm, nanometers; W, wavelength.

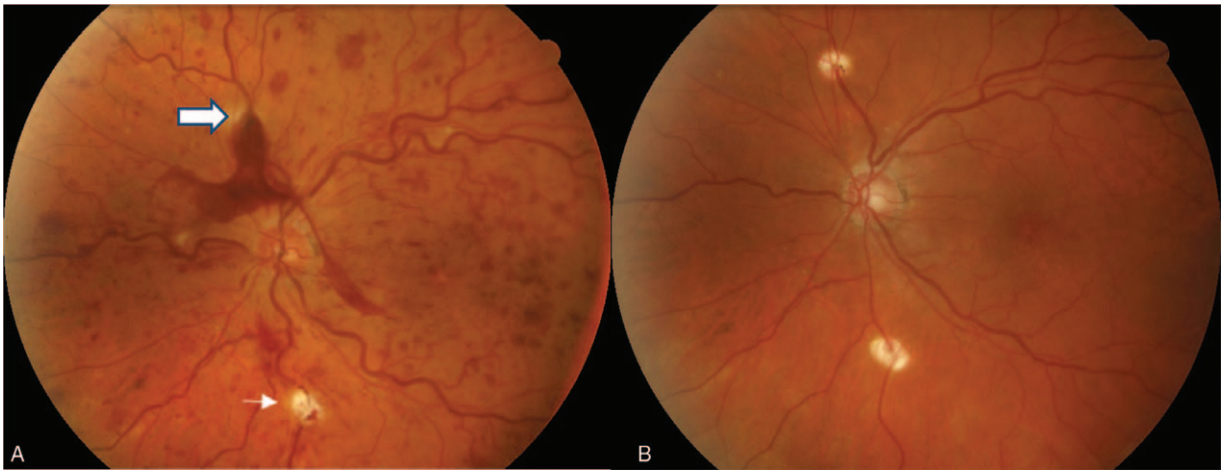

FIGURE 2. CRVO. A, At L-CRA attempt. Two anastomosis sites are seen, above (large arrow) and below (small arrow) the disc. The superior ≥1 hemorrhage from the vein than typically seen with the inferior one more typical of the small amount of blood indicating that the side wall of the vein has been breached. B, 12 months. The superior site has a larger more functional L-CRA with no complications seen from either site. CRVO, central retinal vein occlusion; L-CRA, laser-induced chorioretinal anastomosis

vascular damage to the choroid with the laser energy spreading laterally along the retinal pigment epithelium which limited the likelihood of a vascular connection developing.[41–44] In addition, these studies indicated that the anatomical barriers that needed to be breached included both Bruch membrane and the side of the vein wall. Indeed, once we started using the Nd-YAG to breach the vein wall in cases where the initial argon laser application failed to do so our success rates increased from 33% to 54% (Table 1).[37,38] To reliably puncture Bruch membrane which is one of the anatomical barriers to the successful creation of the L-CRA does require a laser capable of delivering a sufficient power density and this is usually beyond the capability of most conventional lasers.[40,42–45] If the laser is of insufficient power, it will only create a localized full-thickness retinal burn, which may include damage to the internal limiting membrane, without penetrating sufficiently to puncture Bruch membrane. This raises the possibility of localized retinochoroidal neovascularization developing in an eye that has an upregulated level of VEGF acting on a predisposed site .[25,51]

Technique

Preferable sites for the laser application to create the L-CRA are usually a nasal vein or a second-order temporal retinal vein close to its junction with the major quadrantic vein. Two sites are chosen, above and below the horizontal midline, to maximize the chances of a 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 disc as often seen with an acute CRVO (Figs. 1 and 2,).[52] The chosen site should usually be about 2 to 5 disc diameters from the optic disc and if possible, should not exhibit a prominent arterial branch crossing over the venous segment between it and the optic disc. 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 disc, thereby leaving the L-CRA to drain effectively only a segment of the retinal circulation (Fig. 1B). Indocyanine green angiography before the laser application is useful to pick an area where there is a higher density of choroidal vessels. Watershed areas in the choroidal vasculature do exist and it is better to avoid these to ensure that the laser application is done in an area where there is sufficient density of the choriocapillaris to allow the anastomosis to develop. 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. This is to allow the full power of the laser to penetrate to Bruch membrane as the overlying vein has the ability to absorb considerable amounts of laser energy causing a superficial laser burn and preventing the full power penetrating.[42–45] With the Ellex laser the power is usually set to between 2.5 and 3.5 W depending on the degree of cataract, media opacity, and retinal edema. The laser spot size is set to 50 μm, duration to 0.1 second, and the applied through the central portion of a 3 mirror contact lens. The first laser application usually causes some heat constriction of the adjacent vein and often, but not always, a small bubble or cavitation is seen in the choroid. There is no reliably defined endpoint to creating the rupture in Bruch membrane; however, with these power levels we have ascertained that it does occur in virtually 100% of cases.[44,45] The utilization of these power levels is important, as if insufficient power is used, the laser application will only damage the superficial layers of the retina including the internal limiting membrane allowing the potential for neovascularization to occur at the site without penetrating fully to Bruch membrane enabling the anastomosis to form.[42,44] Usually the lower powers are sufficient depending on media opacities; however, if no evidence of disruption is seen in the base of the laser application an additional spot at a higher power level can be applied. Initial applications at the higher power levels are often unnecessary with this laser and may cause more lateral spread of the laser energy causing increased damage to the choroidal vasculature. Caution should also be exercised in those with heavily pigmented fundi and the initial laser application should be set at the lower power levels. It is necessary to allow time to elapse for the vein to partially 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 about 60% of cases this will rupture the vein wall producing a

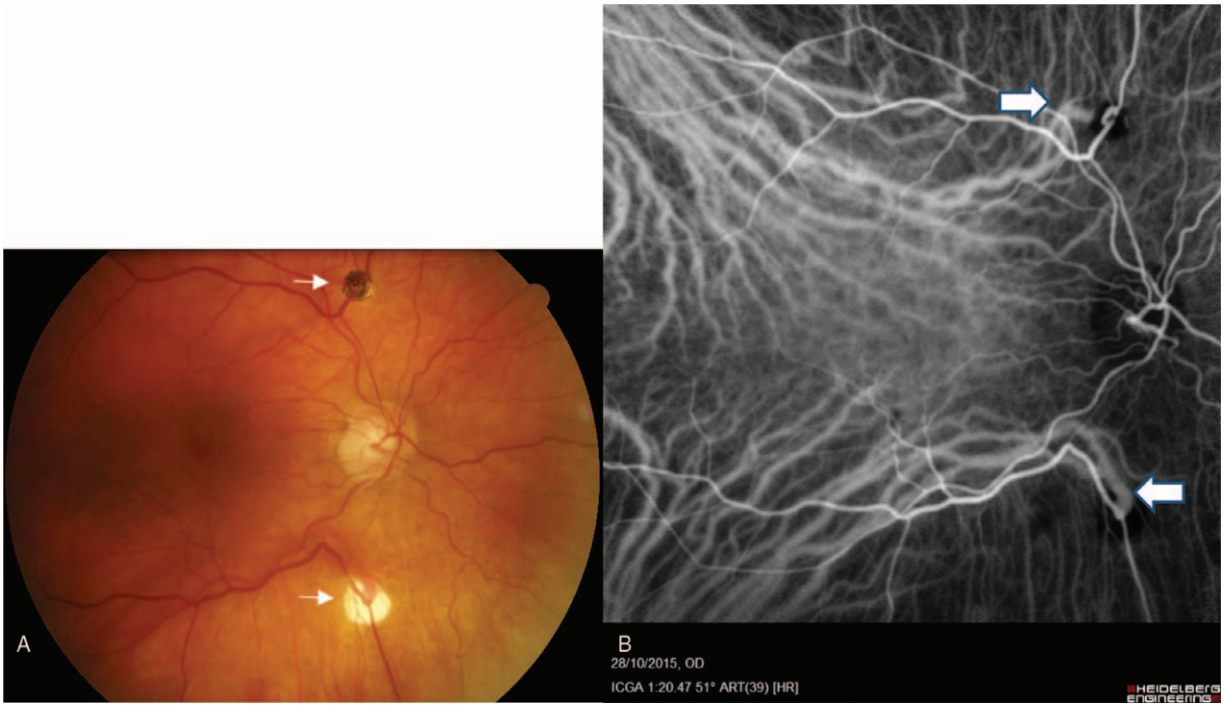

FIGURE 3. CRVO at 12 months post L-CRA. A, Color photo showing 2 L-CRAs (arrows) with the large draining choroidal vessel seen at the inferior site. B, ICG angiogram showing the draining choroidal vessels (arrows). CRVO, central retinal vein occlusion; ICG, indocyanine green angiogram; L-CRA, laser-induced chorioretinal anastomosis.

small amount of visible hemorrhage (Fig. 2A). Time must be allowed to elapse while observing the laser spots for the vein to reopen and this may take several minutes. The hemorrhage from the retinal vein is usually minor and is easily controlled by placing pressure on the eye with the contact lens to the stage where the central retinal artery is closed for up to a minute. If there is no visible hemorrhage from the retinal vein once the vein reopens then a 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 rather than repeating the original 532 nm laser application. Several applications may be required with the end point that is aimed for being a small hemorrhage signifying that the vein wall has been breached. The aim is to breach both Bruch membrane and the side wall of the vein (Fig. 1A, 2A). The L-CRA procedure should not be performed on patients who are significantly anticoagulated. If an anastomosis is to develop it will usually 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 (Fig. 1C, 3B). 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-dependent.[6] Careful follow-up at monthly intervals is very important to monitor the development of the L-CRA and screen for any potential complications. 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 which usually has some retinal ischemia can be treated with sectorial laser photocoagulation making sure to leave at least a disc diameter untreated from the site to avoid damage to choroidal vasculature that may be involved in the developing anastomosis.[38] Retinochoroidal neovascularization from the anastomosis site is very sensitive to intravitreal anti-VEGF agents and is now easily treated with these and can also be controlled by applying sectorial pan retinal laser (PRP).[38,53] Macular edema can be treated with anti-VEGF agents commencing 1 month after the laser attempt while waiting for the anastomosis to fully develop and become hemodynamically significant.

Complications and Their Management

The L-CRA procedure is, in general, safe provided there is careful case selection and rigorous follow-up to treat either vitreous hemorrhages or aberrant retinochoroidal neovascularization occurring from the anastomosis site. The risk of neovascular membranes growing from the site of the attempted anastomosis is significantly associated with increasing retinal ischemia ($P < 0.001$).[38] This was seen in 20% of cases, with a mean time to development of 9 weeks, in an original study conducted before the advent of intravitreal VEGF antagonists and was controlled by rigorous follow-up and prompt treatment to areas of induced or developing retinal ischemia with PRP. The laser anastomosis site, as it often breaches the internal limiting membrane, is susceptible to developing neovascularization especially in eyes with significant levels of retinal ischemia upregulated VEGF.[38,51] The more severe neovascularization that was seen before the development of VEGF antagonists was usually retinal in origin rather than choroidal. The danger of using an underpowered laser that causes damage to the internal limiting membrane without penetrating fully to the level of Bruch membrane is that the patient is exposed to the risk of these without the potential benefit of having an L-CRA development.[38] Avascular fibrous tissue proliferation was also seen in this study in 9% of cases and was not associated with retinal ischemia (Fig. 4). This is similar to an epiretinal membrane seen in premacular fibrosis and is easily peeled via vitrectomy surgery if tractional

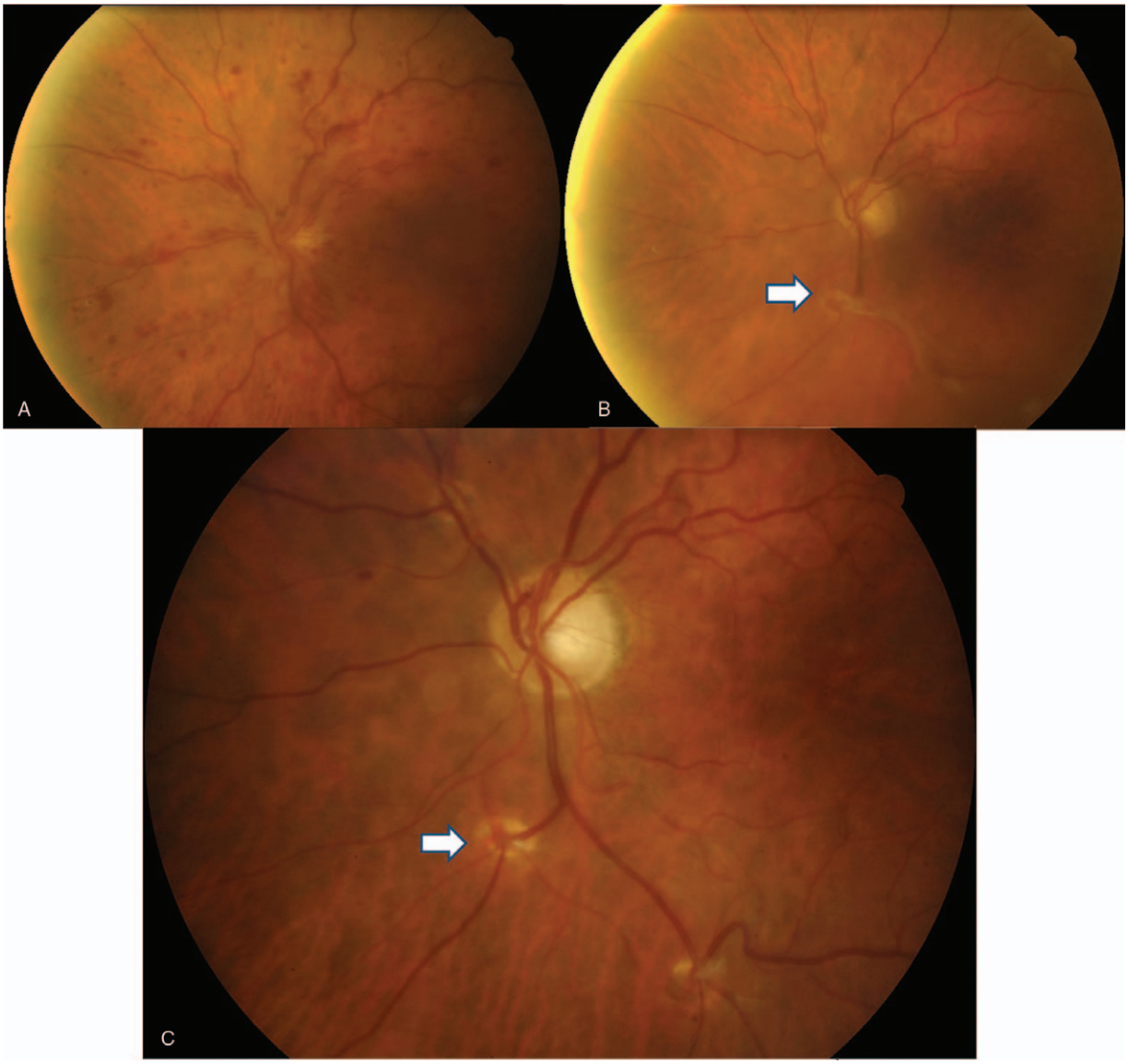

FIGURE 4. A, CRVO at presentation. B, At 8 months showing avascular fibrous tissue extending from the inferior L-CRA site (arrow) and along the inferior vascular arcade. This was causing some tractional effects on the macula. C, 3 months post vitrectomy. The tractional effects have been resolved and the L-CRA site (arrow) and inferior vascular arcade are now well seen. CRVO, central retinal vein occlusion; L-CRA, laser-induced chorioretinal anastomosis

effects are seen on the macular. In the CVBS (again conducted before the advent of anti-VEGF agents) neovascularization was seen at the site of the anastomosis in 18.2% of eyes. It was a protocol requirement for this study that a vitrectomy be performed on any eye with a vitreous hemorrhage sufficient to preclude a view of the retina or any membrane having any tractional effect on the macula and this was performed in 9%.[6,39]

Subsequent to these studies a further randomized study has been conducted comparing the visual and anatomic benefits of combining the L-CRA with an anti-VEGF (ranibizumab) compared with ranibizumab alone.[54] We have previously shown that the neovascular membranes which may occur at the L-CRA site are very sensitive and easily controlled with intravitreal anti-VEGF agents.[53] In this randomized study small areas of neovascularization (<1 disc area) were seen at 10 of a total of 58 sites (17%) in the combination arm, 5 of which regressed spontaneously and the remaining 5 were treated with sectorial PRP peripheral to the L-CRA site. Four patients (13.8%) required vitrectomies with 3 to relieve minor traction on the macula from avascular fibrous tissue emanating from the L-CRA site (two at month 3 and one at month 4) and 1 for a vitreous hemorrhage (occurring at month 23). All 4 patients recovered from the procedure without sequelae.

Although the potential for complications with an L-CRA does remain, we are now able to control these much better, and the risk with a combination approach is significantly smaller. As always the risk of any procedure needs to be weighed against the benefits that it may bring.

COMBINATION APPROACH WITH AN L-CRA AND INTRAVITREAL ANTI-VEGF AGENTS IN THE MANAGEMENT OF CRVO

To fully address the pathogenesis of CRVO and provide a long-lasting cure of this condition, it will require that all of the components that are involved in the retinal venous stagnation, (elevated CVP, cytokine dysregulation) are effectively addressed. As we have discussed earlier, although the advent of effective

intravitreal blockade of VEGF has addressed the dominant cytokine dysregulation, the elevated CVP has remained unaddressed until now. The combination of an L-CRA to the current treatment regimens of VEGF suppression should help address this. The impact of combining these treatments on injection requirements, anatomical outcomes, and BCVA results has been recently examined.[54] In this randomized study which compared the results in the group receiving a combination of an L-CRA and ranibizumab against ranibizumab alone, we were able to create a successful anastomosis in 83% of the combination group. Entry criteria, treatment schedules, and retreatment criteria were based on the central retinal vein occlusion (CRUISE) study.[2] Eligible patients were randomized at baseline into either a combination treatment of L-CRA plus intravitreal ranibizumab or a sham L-CRA plus ranibizumab (29 patients in each group). The L-CRA was attempted at 2 sites above and below the disc and was successful in at least 1 site in 24 of 29 (82.8%) patients in the combination group (15 patients with 2 sites and 9 patients with 1 site), with the remaining 5 being unsuccessful. The patients were treated with ranibizumab commencing 1 month after the L-CRA/sham treatment and received monthly injections for 6 months before moving to monthly pro re nata treatment as per the CRUISE protocol. Overall from month 7 to 24, the mean injections required for each group were 7.1 for the ranibizumab/sham L-CRA and 3.2 for the ranibizumab/total L-CRA ($P < 0.001$). For those in the combination arm with a successful anastomosis (82%) this was reduced to 2.2 injections during this period ($P < 0.001$). This reduction in the injection load was especially apparent in the second year of the study where the mean number of injections required was 4.6 in the ranibizumab/sham L-CRA group versus 1.7 for the ranibizumab/total L-CRA group ($P < 0.001$). When the subgroup with a functioning L-CRA was examined this was found to be reduced to 0.9 injections ($P < 0.001$). After the final mandatory injection at month 7, 34% in the combination group all with a functioning L-CRA did not require any further intravitreal therapy compared with 3% in the ranibizumab alone group ($P < 0.007$).[54]

With regard to BCVA and anatomical outcomes the overall ranibizumab/L-CRA and ranibizumab alone groups were reasonably well matched at baseline with no significant difference. At the conclusion of the study at 24 months, the ranibizumab alone group had an improvement very similar to that seen in the HORIZON study, which was the 2-year extension of the CRUISE study.[4] The mean difference in BCVA at both month 13 and 24 between the 2 overall treatment groups was 8.8 letters (95% confidence interval 0.2–17.3, $P = 0.05$) favoring the group with the combination of treatments.[54] When the subgroup with the functioning anastomosis was compared against the ranibizumab alone group the difference was 12.4 letters ($P = 0.01$). Over the 24 months the change from baseline remained relatively stable for CST, with a reduction of 431.9 μm ($P < 0.001$) and the mean difference between the 2 overall treatment groups estimated as 90.9 μm ($P = 0.01$), in favor of the combination therapy.[54] A post-hoc analysis of the effect of a successful anastomosis on the CVP was conducted with the results showing that those in the combination group with a successful anastomosis (82.5%) had a very significant reduction in CVP compared with the ranibizumab alone group ($P < 0.0001$) (unpublished data).

CONCLUSIONS

Treatment results for CRVO, which result from an obstruction to retinal venous outflow in a closed loop circulation where there is no natural collateral circulation, have improved dramatically with the advent of intravitreal therapies. These results although impressive only address the sequelae of the obstruction to venous outflow and a causal-based treatment has remained elusive until now. The L-CRA provides option of bypassing the obstruction to venous outflow by diverting retinal venous blood from a high pressure obstructed retinal circulation to a low-pressure unobstructed choroidal vein. This can be performed in most cases of CRVO and does result in improved outcomes over the natural history of CRVO and especially when used in combination with existing intravitreal anti-VEGF therapies. The L-CRA does directly address the causal pathology and offers the possibility of a permanent cure for this condition.

It is a complementary treatment to existing intravitreal anti-VEGF therapies. When used in addition to these, the L-CRA does result in significantly reduced injection loads and durations of treatment, together with improved BCVA and anatomical outcomes.[54] The procedure does have some risk; however, provided there is appropriate case selection and careful follow-up, these are reduced to a minimum and are easily treated. The main limiting factor to the more widespread adoption of this technique has been the lack of availability of a laser with appropriate power densities to reliably create the L-CRA. This has been a critical issue as the use of an underpowered laser will create the risk of neovascularization occurring at the laser site by damaging the internal limiting membrane without the benefit of an L-CRA developing, if the power has not been sufficient to breach Bruch membrane. This has been rectified with the production of a purposed designed laser by Ellex (Adelaide, Australia) the Integre Plus.[47]

REFERENCES

1. Liebreich R. Ophthalmoskopishe notizen: ueber die farbe des augengrundes. *Albrecht Von Graefes Arch Ophthalmol*. 1855;1:333–356.
2. 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.
3. 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 3 study. *Ophthalmology*. 2011;118:2041–2049.
4. 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.
5. 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.
6. McAllister IL, Gillies M, Smithies L, et al. The Central Retinal Vein Bypass Study: a trial of laser-induced chorioretinal venous anastomosis for central retinal vein occlusion. *Ophthamology*. 2010;117:954–965.
7. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia: the Blue Mountain Eye Study. *Arch Ophthalmol*. 1996;114:1243–1247.

8. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc*. 2000;98:133–141.
9. Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117:313–319.
10. McIntosh RL, Rogers SL, Lim L, et al. Natural history of central retinal vein occlusion: an evidence-based systematic review. *Ophthalmology*. 2010;117:1113–1123.
11. Hayreh SS. Classification of central retinal vein occlusion. *Ophthalmology*. 1983;90:458–474.
12. Central Vein Occlusion Study Group. Baseline and early natural history report: the Central Vein Occlusion Study. *Arch Ophthalmol*. 1993;111:1087–1095.
13. 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.
14. Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. *Arch Ophthalmol*. 1997;115:486–491.
15. Hayreh SS, Podhajsky PA, Zimmerman MB. Natural history of visual outcome in central retinal vein occlusion. *Ophthalmology*. 2011;118:119–133.
16. Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. *Trans Am Ophthalmol Soc*. 1981;79:371–442.
17. Taylor AW, Sehu W, Williamson TH, Lee WR. Morphometric assessment of the central retinal artery and vein in the optic nerve head. *Can J Ophthalmol*. 1993;28:320–324.
18. Williamson TH. A "throttle" mechanism in the central retinal vein in the region of the lamina cribrosa. *Br J Ophthalmol*. 2007;91:1190–1193.
19. Kang M, Balaratnasingam C, Yu PK, et al. Morphometric characteristics of central retinal artery and vein endothelium in the normal human optic nerve head. *Invest Ophthalmol Vis Sci*. 2011;52:1359–1367.
20. Hayreh SS. Prevalent misconceptions about acute retinal vascular occlusive disorders. *Prog Retin Eye Res*. 2005;24:493–519.
21. Beaumont PE, Kang HK. Pattern of vascular nonperfusion in retinal venous occlusions occurring within the optic nerve with and without optic nerve head swelling. *Arch Ophthalmol*. 2000;118:1357–1363.
22. Weiss JN, Bynoe LA. Injection of tissue plasminogen activator into a branch retinal vein in eyes with central retinal vein occlusion. *Ophthalmology*. 2001;108:2249–2257.
23. Bynoe LA, Hutchins RK, Lazarus HS, Friedberg MA. Retinal endovascular surgery for central retinal vein occlusion: initial experience of four surgeons. *Retina*. 2005;25:625–632.
24. 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.
25. 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.
26. 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.
27. 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.
28. Krohne TU, Liu Z, Holz FG, Meyer CH. Intraocular pharmacokinetics of ranibizumab following a single intra-vitreal injection in humans. *Am J Ophthalmol*. 2012;154:682–686.
29. McAllister IL, Vijayasekaran S, Chen SD, Yu DY. Effect of triamcinolone acetonide on vascular endothelial growth factor and Occludin levels in branch retinal vein occlusion. *Am J Ophthalmol*. 2009;147:838–846.
30. 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.
31. Jonas JB, Harder B. Ophthalmodynamometric differences between ischemic vs nonischemic retinal vein occlusion. *Am J Ophthalmol*. 2007;143:112–116.
32. Spaide RF. Volume-rendered optical coherence tomography of retinal vein occlusion pilot study. *Am J Ophthalmol*. 2016;165:133–144.
33. 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.
34. 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.
35. Campochiaro PA, Hafiz G, Channa R, et al. Antagonism of vascular endothelial growth factor for macular edema caused by retinal vein occlusions: two-year outcomes. *Ophthalmology*. 2010;117:2387–2394.
36. Larsen M, Waldstein SM, Priglinger S, et al. Sustained benefits from ranibizumab for central retinal vein occlusion with macular edema: 24-month results of the CRYSTAL study. *Ophthalmol Retina*. 2018;2:134–142.
37. McAllister IL, Constable IJ. Laser-induced chorioretinal venous anastomosis for treatment of nonischemic central retinal vein occlusion. *Arch Ophthalmol*. 1995;113:456–462.
38. McAllister IL, Douglas JP, Constable IJ, Yu D-Y. 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.
39. 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.
40. McAllister IL, Smithies LA, Previn V. Technique of laser chorioretinal anastomosis creation in central retinal vein occlusion and success rate with a new photocoagulator system. *Retina*. 2016;36:1971–1978.
41. 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.
42. 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.
43. 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.
44. 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 Ophthalml.* 1998;236:174–181.
45. 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.

46. Browning DJ, Antoszyk AN. Laser chorioretinal venous anastomosis for nonischemic central retinal vein occlusion. *Ophthalmology*. 1998;105:670–679.
47. Fekrat S, Goldberg MF, Finkelstein D. Laser-induced chorioretinal venous anastomosis for nonischemic central or branch retinal vein occlusion. *Arch Ophthalmol*. 1998;116:43–52.
48. Kwok AK, Lee VY, Lai TY, Hon C. Laser induced chorioretinal venous anastomosis in ischaemic central retinal vein occlusion. *Br J Ophthalmol*. 2003;87:1043–1044.
49. Lu N, Wang NL, Li ZH, Wang GL, Zhang F, Peng XY. Laser-induced chorioretinal venous anastomosis using combined lasers with different wavelengths. *Eye (Lond)*. 2007;21:962–967.
50. Leonard BC, Coupland SG, Kertes PJ, Bate R. Long-term follow-up of a modified technique for laser-induced chorioretinal venous anastomosis in nonischemic central retinal vein occlusion. *Ophthalmology*. 2003;110:948–954.
51. Pan J, Chen D, Yang X, et al. Characteristics of neovascularization in early stages of proliferative diabetic retinopathy by optical coherence tomography angiography. *Am J Ophthalmol*. 2018;192:146–156.
52. Chopdar A. Dual trunk central retinal vein incidence in clinical practice. *Arch Ophthalmol*. 1984;102:85–87.
53. 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.
54. McAllister IL, Smithies LA, Chen FK, et al. Two-year efficacy of ranibizumab plus laser-induced chorioretinal anastomosis vs ranibizumab monotherapy for central retinal vein occlusion: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136:1391–1397.