Treatments for Central Retinal Vein Occlusion

There is no established standard of care for CRVO. Anti-VEGF therapy may become a first-line choice in the near future.

BY MOTOHIRO KAMEI, MD, PHD

Currently there is no established standard of care for central retinal vein occlusion (CRVO). The conditions that are targeted by current treatments are neovascularization and macular edema. Panretinal photocoagulation (PRP) is accepted as an established treatment for neovascularization, but a consensus has not yet been reached on the indications for and timing of the procedure. Recent large-scale clinical trials have shown anti-VEGF therapy to be effective for the management of macular edema, but the benefits are limited and the long-term effects are unknown.

The available treatments for CRVO include PRP, anti-VEGF therapy, intravitreal injection of steroids, intravitreal injection of tissue plasminogen activator (tPA), and pars plana vitrectomy. Figure 1 shows my algorithm for the choice of these treatment options. This article discusses the most effective available strategies for the treatment of CRVO and provides an overview of promising therapies under investigation.

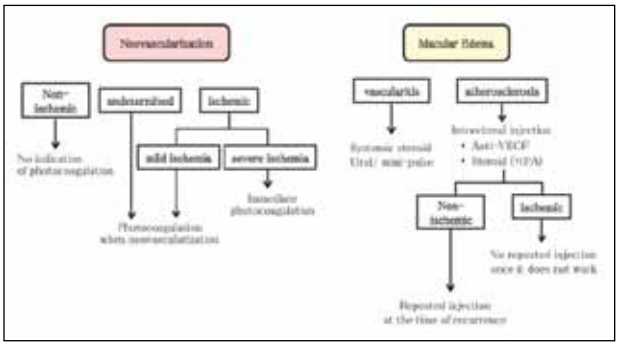

Figure 1. Algorithm for treating CRVO.

NEOVASCULARIZATION

Laser photocoagulation is an established treatment for neovascularization; however, the exact indication for and timing of the treatment in CRVO is still uncertain.

Indication. Nonischemic CRVO, which makes up about 80% of CRVO cases, is not an indication for laser photocoagulation because neovascularization will not occur in these cases. A recent study showed that most cases of CRVO with visual acuity of 0.2 or better are nonischemic,[1] meaning there is no indication for laser treatment. Photocoagulation is indicated in ischemic CRVO, but the timing of treatment is still controversial.

Timing of Photocoagulation. The Central Vein Occlusion Study (CVOS)[2] recommends careful observation of ischemic CRVO, with application of laser treatment immediately after iris, angle, or retinal neovascularization develops. The CVOS does not recommend prophylactic photocoagulation, as neovascularization occurs in only about 30% of ischemic cases (7% to 16% of total CRVO cases).[1,2]

In Japan, however, the application of PRP has been recommended as soon as a case is diagnosed as ischemic or indeterminate. Although I agree with this protocol, as the prognosis is poor once iris or angle neovascularization has developed and intraocular pressure has become elevated, treatment can be withheld until neovascularization is observed because anti-VEGF therapy has recently improved the prognosis of cases in the open-angle stage.

Therefore, I propose a new treatment strategy, classifying ischemic CRVO into 2 subclasses: severe ischemia and mild ischemia. I recommend immediate PRP in severely ischemic cases that show multiple cotton wool spots, dark red color of retinal veins, or more than 30 disc areas of nonperfusion. Larsson and Andréasson[3] provided a useful indication of severe ischemia: Cases with implicit time of 37 msec or longer in photopic flicker electroretinogram (ERG) developed iris neovascularization at 100%. Yasuda et al[4] also demonstrated that the implicit time of flicker ERG was significantly correlated

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with aqueous VEGF concentration. For cases with mild ischemia in undetermined cases, we can withhold photocoagulation and maintain careful observation. Once neovascularization is observed, PRP should be applied with or without anti-VEGF treatment, depending on the severity of iris or angle rubeosis. Considering the incidence of severe ischemia, PRP will be needed in only one-tenth of total CRVO cases or less.

Procedures for Laser Application. Treatment usually starts in the periphery, avoiding areas of retinal hemorrhage because applying laser to hemorrhagic areas causes excessive burns and severe damage to the nerve fiber layer. After a period of months waiting for dense hemorrhages to absorb, photocoagulation can be added to the area with disappearing hemorrhage. However, it is better to apply PRP immediately if cases develop severe ischemia, as previously mentioned. In cases with severe ischemia, laser irradiation can be applied even to the area of hemorrhage, but it should be restricted to the midperipheral to peripheral area and should be avoided around the optic nerve head because of the high density of nerve fibers. Extra attention is required when a pattern scanning laser such as the PASCAL (Topcon) is applied in eyes with severe ischemia; one must decrease the spacing and make the burn pattern dense, or the treatment will fail to prevent development of neovascular glaucoma (Figure 2).

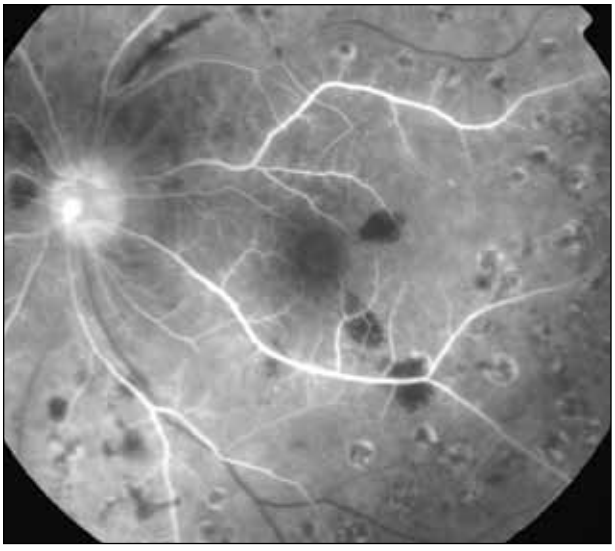

Figure 2. Fluorescein angiogram of an ischemic CRVO shows that the perfusion is severely delayed (at 51 seconds after injection). Note the density of photocoagulation, which was not enough to prevent neovascularization. Neovascular glaucoma subsequently developed in this case.

MACULAR EDEMA

Currently, there is no positive indication for treatment of macular edema in ischemic CRVO because visual improvement will not be achieved even though the edema will regress.

Medical Treatments. There is only weak evidence of beneficial effects for antiplatelet or anticoagulant agents in CRVO, and these treatments can also have adverse effects on vision; therefore, the use of these types of drugs in CRVO is not recommended.[5] The efficacy of intravitreal triamcinolone acetonide injection[6] and dexamethasone intravitreal implant[7] have recently been shown in randomized clinical trials.

Both the anti-VEGF antibody ranibizumab (Lucentis, Genentech)[8] and the soluble VEGF receptor aflibercept (Eylea, Regeneron)[9] have been shown to significantly reduce macular edema and improve visual acuity in CRVO in randomized studies. Although these drugs showed efficacy with repeated intravitreal injections in clinical trials, a reduction in the number of treatments administered in practice is desirable to reduce the psychological and financial burdens placed on patients. However, practical protocols, such as criteria for reinjection or cessation of therapy, have not been established yet.

Considering that VEGF is necessary for regeneration of vascular endothelial cells, the potential for negative interference by anti-VEGF drugs should be investigated, especially regarding anti-VEGF therapy applied in the early phase of CRVO. There is controversy over this issue; 1 report showed that nonischemic CRVO progressed to ischemic CRVO after early anti-VEGF treatment, while Campochiaro et al[10] recently reported that anti-VEGF treatment did not worsen retinal perfusion in the CRUISE study. Most patients in the CRUISE study were nonischemic, and the mean time from diagnosis to screening was 3.3 months, indicating the treatment must have performed at more than 4 months after disease onset.

Therefore, the exact timing of anti-VEGF therapy has yet to be established, although less than 6 months after onset seems better, as the group receiving sham injection during the first 6 months and as-needed (prn) treatments after 6 months in the CRUISE study showed worse visual results than the group treated monthly in the first 6 months followed by prn treatments.[8] However, results

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Which treatment option do you consider best for the management of macular edema associated with CRVO?

- ☐ Intravitreal triamcinolone acetonide injection
- ☐ Dexamethasone intravitreal implant
- ☐ Ranibizumab
- ☐ Aflibercept
- ☐ None of the above

of extended observation of the anti-VEGF clinical trial (HORIZON)[11] showed no significant difference between the immediate treatment groups and the delayed treatment group at 2 years after the onset.

Photocoagulation. The prospective, randomized CVOS trial concluded that grid laser photocoagulation for macular edema associated with CRVO was effective for reducing edema but did not improve visual acuity.[12] The investigators posited that the reason no visual improvement was achieved, despite the reduction of edema, could be that photocoagulation may cause irreversible damage to the inner retina. Following these results, photocoagulation for macular edema in CRVO has not been recommended. In fact, observation, not photocoagulation, was employed as the control in recent clinical trials such as SCORE and CRUISE.[6,8]

Surgery. Even in the era of drug therapy, pars plana vitrectomy is still performed in CRVO with persistent macular edema. Although there have been no large multicenter, randomized, prospective trials providing evidence that vitrectomy is significantly effective for macular edema associated with CRVO, creating the posterior vitreous detachment with or without internal limiting membrane peeling may relieve traction on the macula or remove cytokines, including vascular endothelial growth factor. Only eyes with nonischemic CRVO showed visual improvement in a study reporting visual recovery in two-thirds of patients.[13]

PROMISING THERAPIES

Simultaneous intravitreal injection of triamcinolone acetonide and tPA demonstrated significant ($P < .001$) reduction of macular edema (from 1072 µm at baseline to 409 µm at 12 months) and improvement of vision (3 lines or more in 53% at 12 months).[14] The average number of injections during 12 months was 2.5, which is much less than with anti-VEGF drugs.

We have investigated the use of direct focal laser application to leak points, dilated capillaries, and microaneurysms, located at the edge of the foveal avascular zone and around the macula. In preliminary investigations, we performed leak point direct photocoagulation in 17 eyes with macular edema refractory to anti-VEGF therapy and traditional grid pattern photocoagulation and obtained a mean reduction of edema from 469 µm at baseline to 360 µm ($P = .0003$).

Kadonosono and colleagues have developed a specially designed ultrathin needle for endovascular surgery. Using this needle, they inject balanced saline solution into retinal veins to flush the thrombus in CRVO. A prospective clinical trial is under way, and the technique seems to be very effective (personal communication).

CONCLUSION

Anti-VEGF therapies will become the first choice of treatment for CRVO over the next few years. However, adverse effects of these drugs on endothelial cell regeneration should be investigated as soon as possible. Indications for prophylactic photocoagulation to severe ischemic CRVO should be established. ■

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