THE ROLE OF LASER IN THE PHARMACOLOGIC ERA OF RETINA

Laser still plays a prominent part in managing retinal pathologies, and innovations in laser delivery suggest potential areas where indications might be expanded.

BY BARUCH KUPPERMANN, MD, PHD

Although the retina subspecialty has largely embraced pharmacology in the treatment of patients with retinal diseases, laser therapy continues to play important roles in managing the various pathologies routinely encountered in the clinic. Having a variety of treatment options with different mechanisms of action at our disposal increases the likelihood of achieving successful outcomes for patients.

On the whole, medical management of many retinal diseases has dramatically improved our ability to stop and even reverse anatomic deficits and restore vision. However, medical therapy is not universally effective, nor is it always the best option for treating a particular clinical manifestation. Thus, laser remains an important treatment option, even in the era of pharmacology, and especially as new forms of laser therapy (ie, subthreshold and micropulse laser) make delivery of laser energy to sensitive retinal tissues both safer and more effective. This article reviews the two main disease areas in which laser therapy still plays an important role.

AT A GLANCE

- Laser may be effective as adjunctive therapy to reduce the need for repeat anti-VEGF injections in patients with diabetic eye disease.
- The visual potential of the eye and the patient's need for recurrent anti-VEGF injections may determine whether laser therapy is appropriate in the treatment of BRVO and CRVO.
- Laser remains an important treatment option in managing retinal pathologies, even in the era of retinal pharmacology.

LASER IN DIABETIC EYE DISEASE

Extrafoveal DME

Perhaps the most obvious application for laser in retina practice is in eyes with extrafoveal diabetic macular edema (DME). Two anti-VEGF agents approved by the US Food and Drug Administration (and one used off label) for this indication are well established as gold standard therapies for center-involved DME, but they have not been tested in rigorous clinical trials for DME that does not involve the fovea. The only modality that has been tested and proven effective for non–center-involved DME is focal photocoagulation. The ETDRS study established that patients with clinically significant macular edema treated with focal argon laser photocoagulation were statistically significantly less likely to lose vision and more likely to gain vision than untreated patients.[1]

At the time of the ETDRS, and in the absence of viable alternatives to laser, the photodestructive side effects of focal and grid laser were more acceptable. Treating retinal pathologies with laser was seen as a viable way to minimize the potential for the anatomy to worsen, even at the risk of possible scotoma and scarring of the retina. In the modern era, however, that paradigm has shifted. Now, leaving patients with compromised visual potential is less acceptable and compliant patients can be followed until foveal involvement is evident, at which time anti-VEGF therapy can be offered. As a result, there is less of a barrier to treating extrafoveal DME than there was in the past, and it might seem that laser is less important in the overall management of patients with DME.

On the contrary, however, innovations in laser therapy may now allow patients to benefit from laser treatment without the risk of potential photodestructive side effects. For example, it is possible to use subthreshold laser levels to deliver energy to the eye without causing scars or

permanent damage.[2] The exact mechanism of action of subthreshold laser is unknown, but it is thought that it may stimulate the retinal pigment epithelium to release trophic factors, inciting a restorative response in addition to a therapeutic benefit. If it can be substantiated that subthreshold and/or micropulse laser delivers laser energy to the site of pathology in DME without causing scarring or loss of visual potential, then these modalities may be considered viable treatment strategies for patients with foveal DME.

There is some suggestion that standard thermal laser may be effective as adjunctive therapy to reduce the need for repeat anti-VEGF injections. In the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I study, for example, patients who received laser required three fewer injections of anti-VEGF therapy, although there was no benefit for laser in terms of additional improvement in vision.[3]

Poor Responders

Another indication for laser therapy in eyes with DME is for patients who exhibit a suboptimal response to anti-VEGF therapy. The DRCR.net Protocol T study demonstrated significant benefits of anti-VEGF therapy in terms of anatomic and functional response, and yet 56%, 46%, and 37% of individuals treated with bevacizumab (Avastin, Genentech), ranibizumab (Lucentis, Genentech), and aflibercept (Eylea, Regeneron), respectively, received per-protocol rescue laser after 24 weeks.[4] This study provides evidence that anti-VEGF therapy may reach a plateau and that additional measures may be necessary to restore anatomy and visual potential.

DR in the Presence of DME

Recently, ranibizumab and aflibercept gained label indications for the treatment of diabetic retinopathy (DR) in the presence of DME. In a subset analysis of the pivotal RISE and RIDE studies,[5] the time to progression to proliferative DR (PDR) was significantly reduced among patients treated with ranibizumab, and many patients experienced improvements in ETDRS retinopathy classification scores.

In the VIVID and VISTA trials, roughly a third (33-34%) of eyes treated with aflibercept had reductions in DR severity.[6,7] It is important to note that, although these agents are approved for treatment of DR in the presence of DME, there is no clinical trial evidence that they would be effective against DR without concomitant DME. That indication is being studied in clinical trials.

For patients with milder forms of DR in the presence of DME and those with DR who are willing to return to the clinic for regular monitoring, deferring laser may be a plausible strategy. However, compliance with medical protocols is often less than ideal in patients with diabetes, and there is suggestion from an analysis of a large claims database that in real-life practice, patients with DME may receive as few as two to four injections per year while visiting their ophthalmologist between four and six times each year.[8] Thus, offering treatments that can minimize reliance on patient compliance is prudent and often necessary. Laser therapy, especially micropulse and subthreshold modalities, may offer such an option for these patients.

> **"Laser has a more explicit role in PDR, which, in advanced stages, is associated with vitreous hemorrhage, scar tissue formation that can lead to tractional retinal detachment, and neovascular glaucoma ... .**

PDR

Laser has a more explicit role in PDR, which, in advanced stages, is associated with vitreous hemorrhage, scar tissue formation that can lead to tractional retinal detachment, and neovascular glaucoma, all secondary to retinal ischemia. Panretinal photocoagulation (PRP) is considered a primary treatment option in PDR to ablate peripheral retina so as to reduce VEGF release and subsequent neovascularization. Anti-VEGF therapy has been studied as an alternative to laser therapy in PDR[9]; however, PDR and DME often present simultaneously in eyes with advanced diabetic eye disease. These types of cases often require multiple layers of treatment that may include vitrectomy, laser, and anti-VEGF therapy to blunt new vessel formation.

LASER IN THE TREATMENT OF RVO

Laser continues to be valuable in managing certain cases of branch (BRVO) and central retinal vein occlusion (CRVO). In the presence of neovascularization that involves the retina, iris, or angle, full PRP for CRVO or sector PRP for BRVO will prevent further progression and induce regression of neovascularization in most cases. Prompt PRP is also indicated to prevent damage due to neovascular glaucoma secondary to CRVO, although intravitreal anti-VEGF therapy is often used in combination with PRP to achieve the most effective results, both in terms of speed of initial effect (from the anti-VEGF agent) and maintenance of regression of neovascularization

(from the durability of effect of laser PRP).

Focal/grid laser to areas of leakage may be of benefit in the subset of eyes treated with anti-VEGF therapy for macular edema secondary to RVO in which the pharmacologic treatment does not provide benefit. Ultimately, the visual potential of the eye and the need for frequent recurrent anti-VEGF injections may be the determining factor in whether laser therapy is appropriate in the treatment of BRVO and CRVO.

CONCLUSION

Although the growth of pharmacology in retinal medicine has been an advantage for patients, the need for repeated injections could adversely affect patients' quality of life or willingness to comply with treatment. New treatment approaches that are easier to comply with or that reduce the treatment burden are needed, as are alternative treatment approaches for patients who do not respond to anti-VEGF therapy. Due to the highly variable nature of some retinal pathologies, laser may also play a prominent role in their management.

Newer innovations in laser technology, notably micropulse and subthreshold laser, offer promise for expanding the role of laser, either as primary therapy or as an adjunct, to potentially reduce the need for repeated anti-VEGF injections. In some pathologies, such as PDR, laser therapy—even photodestructive forms—may stop progression and induce regression. ■

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