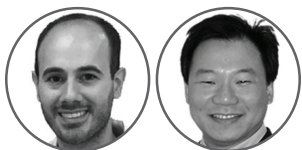


SubLiminal Laser for Center-Involving Diabetic Macular Edema

BY ALEJANDRO FILLOY-RIUS, MD, PHD, FEBO, AND VICTOR CHONG MD, FRCS, FRCOPHTH



Diabetic retinopathy (DR) is a major microvascular complication of diabetes. It is estimated that by 2030, nearly 200 million people will be affected by this disease.¹ During this period, vision-

threatening DR will increase from 37 million to 56 million people globally.¹ Center-involved diabetic macular edema (CI-DME) is the most common cause of decreased visual acuity in DR patients, affecting more than 750,000 patients in the United States alone.²

TREATMENTS FOR DME: PAST AND PRESENT

Today's treatment landscape offers several options for treating CI-DME. Currently, the standard of care for diabetic macular edema (DME) treatment-related conditions, including CI-DME, is serial intravitreal injections of anti-VEGF drugs. Though proven successful anti-VEGF therapies are expensive and require an arduous timetable of regularly scheduled office visits for repeat injections. Furthermore this regimen has been associated with a portfolio of issues, including residual edema in 25 to 64% of eyes³ and is not devoid of complications. This process may be difficult for patients to maintain. In lower socio-economic countries with limited resources, access to expensive anti-VEGF therapy may not be an option and is unaffordable to many populations and health care systems.

CI-DME may be caused either by inflammation/exudation, by ischemia, or by a combination of both. In the foveal avascular zone, the only mechanism for extracellular fluid resorption is the retinal pigment epithelial (RPE) pump, which may explain the more significant accumulation of edema fluid at this location. A recent study concluded that in 15 to 30% of DME cases, a sub-foveal serous retinal detachment is present.⁴ Laser is a useful tool in the treatment of CI-DME and although less potent than intravitreal therapy, there is no shortage of scenarios, specifically using subthreshold SubLiminal laser therapy in which laser is all you need to safely, effectively, and efficiently control CI-DME. We will summarize these in the next section but they all show that the edema is predominantly inflammatory.

SubLiminal laser therapy is a modern subthreshold laser that employs a customizable pattern grid selection and delivers treatment through a succession of short, microsecond-long pulses of a laser instead of the usual "continuous" beam of a conventional laser. This allows the RPE to cool between pulses, preventing a critical amount of heat from accumulating in the tissue and the consequential RPE, as well as retinal scarring which is unnecessary to obtain significant clinical response.

Finally, another treatment approach to CI-DME is vitrectomy with release of macular traction, internal limiting membrane peeling, laser photocoagulation, and perioperative intraocular corticosteroid therapy. Compared to anti-VEGF, vitrectomy is less expensive, reduces the frequency of required office visits, and yields longer-lasting effects. However, a small prospective randomized clinical trial using focal/grid laser as a control arm demonstrated that vitrectomy thins the edematous macula but inconsistently improved visual acuity.⁵

THREE IDEAL CI-DME SCENARIOS FOR SUBLIMINAL LASER TREATMENT

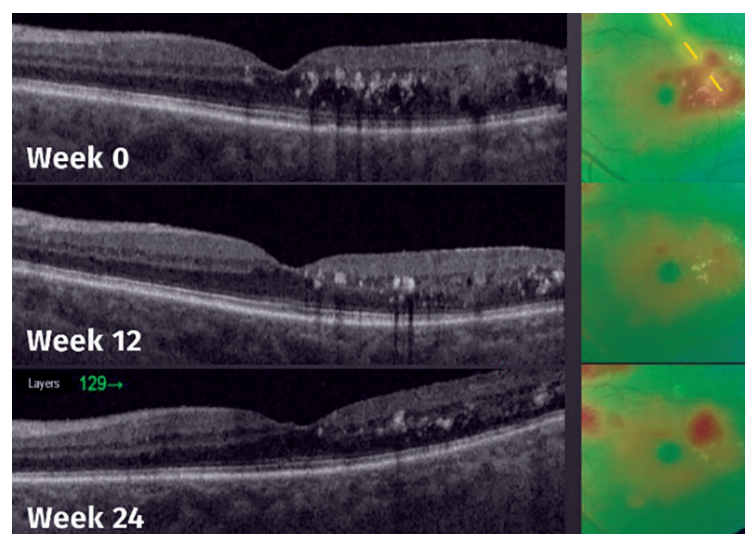


Figure 1. Clinically significant extrafoveal edema.

There are three significant diagnostic scenarios of CI-DME where SubLiminal laser should be considered before any other treatment modality. In my practice and related study,⁶ I use the EasyRet 577-nm yellow SubLiminal laser (Quantel Medical).

The first is clinically significant extrafoveal edema. In these cases, the edema is distant enough from the fovea to keep the central vision safe. The benefits of using SubLiminal laser therapy in cases like this are the durability and repeatability of the laser treatment since there is no damage to the RPE, so the area can be retreated in future edematous resurgences (Figure 1).

The second scenario consists of a fovea-involving case with decreased visual acuity. Here there is an option of combination

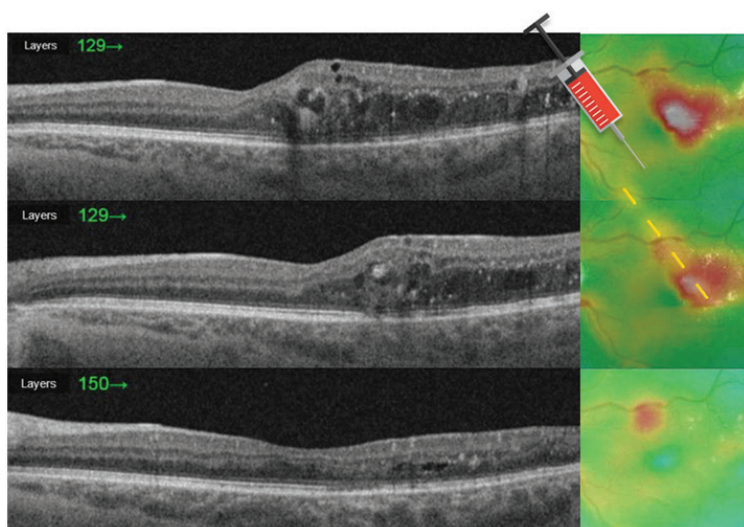


Figure 2. Combination treatment in thicker fovea/decreased visual acuity (inject first).

treatment (laser following intravitreal injection). When the fovea is involved and the vision is reduced, the priority is to “rescue” the fovea from the inflammatory environment to improve the long-term visual prognosis, so intravitreal therapy would be the first-line treatment thanks to its quicker action. We inject first until the edema is cleaned away from the fovea and then laser the remaining thickened area, which will provide a better and more durable response at times with one single injection (example shown in Figure 2).

The third scenario is a fovea-involving mild edema with good vision. In these cases, the treatment decision is more controversial. Is observation the best path forward, risking further deterioration? Should we spend money and risk complications such as endophthalmitis injecting a good eye? Conventional laser should not be considered close to

the fovea. However, SubLiminal laser can work safely next to the fovea and make a significant difference in the growing severity of the edema while reducing or eliminating the need for intravitreal injections. SubLiminal laser is, in our opinion, the best option for this scenario and has proven effective in a range of cases with low levels of complications (Figure 3).⁵

We performed a study which demonstrated success in terms of safety and efficacy, and it stabilized visual acuity for these patients.⁶ From week 1 to week 12, the central retinal thickness decreased an average of 16 μm ($P = .001$), and from week 1 to the end of follow-up, we saw an average decrease of 22 μm ($P = .0003$). OCT showed the edema had completely resolved in 30% of the cases after the first SubLiminal laser therapy treatment and significantly improved for 50% of the cases. At the end of the follow-up, a total of 56% of the cases were resolved. None of the treated patients experienced deterioration requiring a shift to combination intravitreal treatment during the follow-up.

SUBLIMINAL LASER TREATMENT—HOW IT IS DONE

For CI-DME, it is recommended to follow the guidelines provided by Victor Chong MD, FRCS, FRCOphth, the leading research physician and industry expert in SubLiminal laser therapy of DME. First, it is essential to treat large areas to stimulate a high number of RPE/Müller cells to obtain a clinically significant response. For the same reason, treat densely and avoid leaving blank spaces so that you can recruit every cell in the treatment area. Lastly, it is recommended to use the appropriate amount of power. Too much energy per area unit will result in a “suprathreshold” treatment that may result in cell damage. Titration of power at one-half of the minimum energy to cause a barely visible burn in the healthy peripheral macula is recommended. Since the term “barely visible” is quite subjective, it might be safer for the beginner to start at a lower power (i.e 1/3 and work his or her

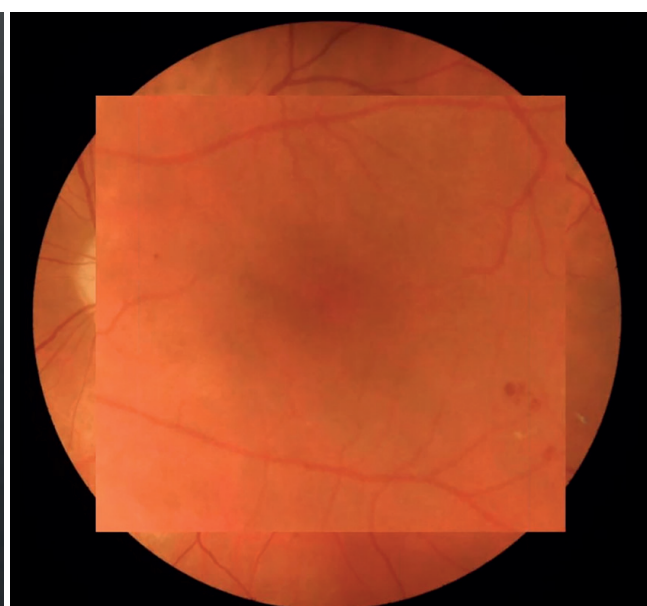
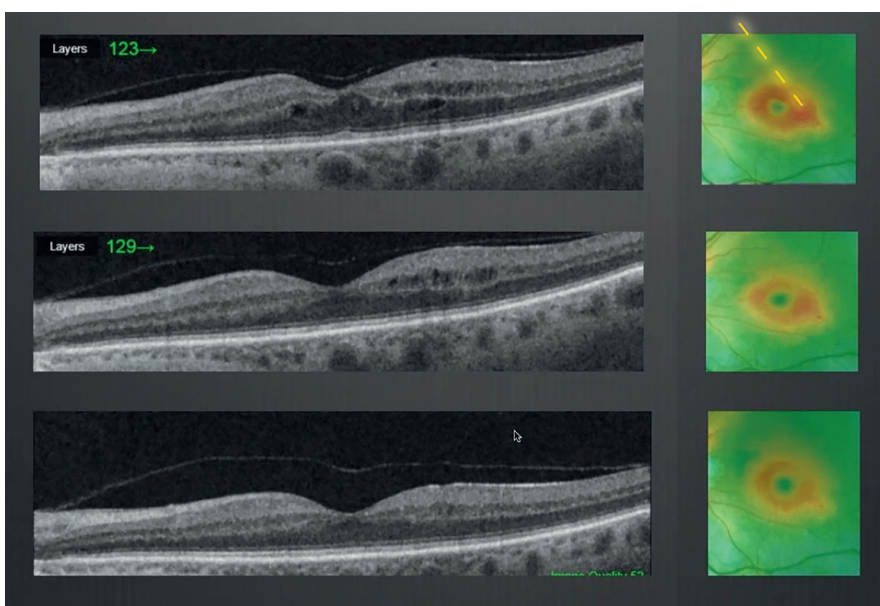


Figure 3. Fovea-involving edema with good vision after SubLiminal laser (< 400 μm thick).

way up from there). The rest of the parameters can be universalized (spot size 160 μm , 5% duty cycle). Following these recommendations will avoid insufficient spots, which has been identified as the primary cause for treatment failure.⁷

SHOULD WE TREAT THE FOVEA? HOW CLOSE CAN WE GO?

This question has two correct answers. First, if the recommended treatment guidelines are followed precisely, treating through the fovea is possible and safe. Nevertheless, Dr. Chong does not recommend transfoveal treatment, especially for new SubLiminal laser users and particularly in cases of DME in which we are treating OCT-guided treatment areas. Indeed, the fovea is extremely small. After treatment of the areas surrounding the fovea, the beneficial effect of the laser treatment will extend to the foveal area without treating it directly (Figure 4). Adding a few additional laser spots to include the fovea has not been proven to be more effective and should be reserved for physicians with extreme proficiency and expertise. Second, the preferred protocol is to exclude the fovea during treatment as you will see equally satisfying results. You can treat close to the fovea, up to 100 μm . So, can you treat the fovea? Yes. Do you need to? No, the few spots necessary to cover it will hardly make any change in the overall results.

For each case, it is recommended to evaluate at 8 to 12 weeks using both OCT slides and thinness maps, as well as autofluorescence, to check for any RPE disturbances from potential suprachreshold treatment. With that you can adjust your parameters to optimize your results.

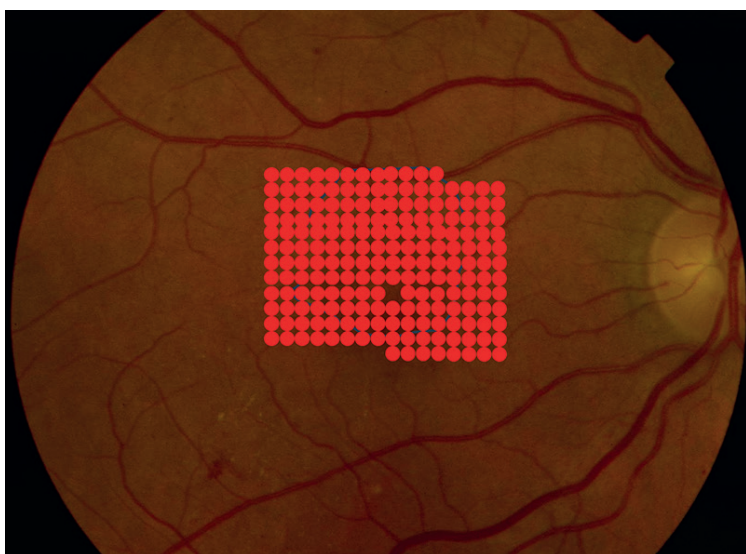


Figure 4. SubLiminal laser treatment excluding the fovea.

CONCLUSION

The main takeaway we learned from our study is that SubLiminal laser is an effective and safe treatment alternative for fovea-involving DME with good vision.⁶ A strong point for new practitioners is sparing the fovea from treatment does not worsen the results while providing extra safety. Choosing to hold off treatment to observe will require a high frequency of follow-up visits. Also, you can expect one-third of observed patients will experience deterioration that will require intra-vitreous treatment.⁸

When considering SubLiminal laser for CI-DME, patient selection is key. SubLiminal laser therapy is a viable first-line treatment option for CI-DME patients with clinically significant extrafoveal edema and patients with fovea-involving mild edema with good vision. SubLiminal laser can reduce, or eliminate, the use of intravitreal injections and associated risks, costs, and a demanding in-office treatment schedule. In our experience, the more we utilize SubLiminal laser therapy for DME, the more encouraging the outcomes are.

DME is a complex disease that requires careful examination, monitoring, and treatment to gain good responses. The two cornerstones to successful SubLiminal laser treatment are surface area and density. It is important to practice patience with this process and to educate the patient on realistic expectations. A flawlessly performed laser takes from 6 to 16 weeks to begin showing its effect, so be patient. Finally, as with any surgical procedure, if you take the time to audit your processes, laser application proficiency, and results, you will get better with time. ■

1. Zheng Y, He M, Congdon N. The worldwide epidemic of diabetic retinopathy. *Indian J Ophthalmol*. 2012;60(5):428-431.
2. Klein R, Klein BE, Moss SE, Cruikshanks KJ. The Wisconsin epidemiologic study of diabetic retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology*. 1995;102:7-16.
3. The Diabetic Retinopathy Clinical Research Network. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372:1193-1203.
4. Browning DJ. *Diabetic Retinopathy, Evidence-Based Management*. 1st ed. Ch. 7. New York: Springer Inc; 2010.
5. Haller JA, Qin H, Apte RS, et al. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. *Ophthalmology*. 2010;117:1087-1093.
6. Filloy, A, Chong, V, Solé E. Subthreshold yellow laser for fovea-involving diabetic macular edema in a series of patients with good vision: effectiveness and safety of a fovea-sparing technique. *BMC Ophthalmol*. 2020;20:266.
7. Lavinsky D, Cardillo JA, Melo LA, et al. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2011;52(7):4314-4323.
8. Baker CW, Glassman AR, Beaulieu WT, et al. Effect of initial management with aflibercept vs. laser photocoagulation vs. observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. *JAMA*. 2019;321(19):1880-1894.

ALEJANDRO FILLOY-RIUS, MD, PHD, FEBO

- Associate Professor of Ophthalmology, Faculty of Medicine, Universitat Rovira i Virgili, Tarragona, Spain
- Retina and cataract specialist, Joan XXIII Hospital, Tarragona, Spain
- Member of the Catalan Society of Ophthalmology and Spanish Retina and Vitreo Society
- alejandروفilloy@gmail.com
- Financial disclosure: Lecture fees (Quantel Medical)

VICTOR CHONG, MD, FRCS, FRCOPHTH

- Consultant Ophthalmic Surgeon, Optegra Eye Hospital, London, United Kingdom
- victor@eretina.org
- Financial disclosures: Consultant (Quantel Medical); employee (Boehringer Ingelheim International GmbH)