MicroPulse Laser Therapy in Refractory Edema

By Sam E. Mansour, MD

The Early Treatment Diabetic Retinopathy Study (EDTRS) Group demonstrated that laser photocoagulation reduced the risk of moderate visual loss from diabetic macular edema (DME) by 50% (from 24% to 12% at 3 years after initiation of treatment). Since that study was published, new pharmacologic options have emerged, as have new modalities for laser treatment. I have found that using a combination of both is most effective when treating patients with macular diseases.

Case study 1
A 62-year-old woman with type 2 diabetes mellitus (DM) presented with previously untreated DME in her right eye. Treatment was initiated with a series of 4-6 weekly injections of bevacizumab (Avastin, Genentech), and the central subfield mean retinal thickness (CSMT) decreased from 388 µm to 268 µm on optical coherence tomography (OCT). Visual acuity improved from 20/60-1 at baseline to 20/40-2. In total, the patient received 5 intravitreal bevacizumab injections. Approximately 4 weeks following the last injection, I performed a single treatment of laser photocoagulation using the 577 nm laser (Iridex) with micro-pulse technology (MPLT). Treatment parameters for the macular grid treatment were as follows: power (320 mW); duty cycle (5%); duration (200 ms); spot size (200 µm); pattern (confluent); and spot count (312). After 2 months time, the patient’s vision improved to 20/25-2, and retinal thickness decreased further to 196 µm as seen on OCT (Figures 1 and 2).

Case study 2
A 57-year-old man with moderately well controlled type 2 DM presented with clinically significant DME in his right eye. He had previously received a single intravitreal triamcinolone injection 4 months prior to his initial visit. His visual acuity at presentation was 20/80-2. A single treatment of MPLT was performed. Treatment parameters for the macular grid treatment were as follows: power (460 mW); duty cycle (5%); duration (200 ms); spot size (200 µm); pattern (confluent); and spot count (214). The patient’s visual acuity improved to 20/30 at 184 days after treatment. I performed no other treatments or injections (Figure 3).

Evolution of Micropulse Laser
Different techniques for tissue-sparing photocoagulation, in order from highest lesion density to lowest, include xenon arc, conventional, modified conventional, subvisible continuous-wave, and subvisible micropulse. Conventional photocoagulation was the technique recommended in the EDTRS treatment guidelines. The
The main idea behind this treatment strategy was that the therapy had to result in the destruction of oxygen-consuming photoreceptors and/or retinal pigment epithelium cells in order to be effective. The treatment endpoint in this modality relied on a visible, high-intensity lesion. The direct heating of tissue causes retinal blanching, tissue destruction, and post-treatment scarring that expands with time. Experimental studies on the indirectly heated tissue surrounding laser lesions found that they produced a stress response, which induced beneficial intracellular biological activity that was antiangiogenic and restorative. This antiangiogenic activity is the result of the upregulation of certain angiogenic inhibitors such as pigment epithelium derived factor (PEDF) and the downregulation of inducers of VEGF. Further studies demonstrated that the changes in gene expression in these surrounding cells contribute to the long-term inhibitory effect of laser photocoagulation.

The discoveries involving the stress-induced antiangiogenic activity in the cells surrounding focal laser therapy led to the technique of modified conventional photocoagulation. The theory behind this approach is to create a barely visible threshold burn, and then lower the laser setting slightly to treat the diseased area. This causes minimal retinal blanching in the directly heated tissue, but still results in some post-treatment scarring that tends to expand with time. The indirectly heated tissue remains viable and produces the same stress response as in conventional photocoagulation.

The theory that oxygen-consuming photoreceptors and retinal pigment epithelium cells had to be destroyed in order to achieve the desired clinical effect has been brought more and more into question. As a result, this opened the door to further exploration of the clinical utility of subvisible micropulse tissue-sparing photocoagulation. Micropulse technology essentially “chops” a continuous-wave laser beam into a train of repetitive short pulses, which allows the treated tissue to cool between pulses and thereby reduces thermal buildup. The entire treatment is maintained at a subvisible level, so that, rather than destroying tissue, it is merely inducing the stress response that results in the antiangiogenic and restorative activity. The reduction in thermal buildup also causes only negligible thermal, expansion, sparing neighboring tissue from heating indirectly.

Clinical studies comparing MPLT and modified ETDRS photocoagulation in clinically significant DME found that both modes of treatment showed stable visual acuity and reduced central retinal thickness. However, retinal sensitivity at central 4° and 12° increased in the micropulse group and decreased in the modified ETDRS group. Long-term studies showed that MPLT was effective with no detectable retinal damage up to 10 years.

![Figure 2. Same patient as Figure 1. OCT scans show additional reduction of central retinal thickness from 268 µm to 196 µm after single MPLT treatment.](image)

![Figure 3. OCT scans showing reduction in retinal thickness corresponding to VA improvement from 20/80 -2 to 20/30 after single MPLT treatment.](image)
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Pharmacologic Treatment
In recent years, treatment of DME has shifted away from laser photocoagulation and toward intravitreal injections of VEGF inhibitors and/or steroids. Although this approach has been found to improve visual acuity and decrease retinal thickness even in cases of diffuse diabetic edema that previously did not respond to photocoagulation, its therapeutic duration is short-lived. Clinicians have found that indefinite monthly injections of anti-VEGF drugs are not optimal for patient care or economics.

Treatment Algorithm
In my experience with the management of DME, combining laser and intravitreal corticosteroids with anti-VEGF therapy is better at reducing macular edema than anti-VEGF agents alone. Anti-VEGF agents no doubt are very effective at reducing the other nonedematous complications of diabetic retinopathy. Using a combination of therapies appears to work best. I have found it convenient to divide DME cases into 3 categories based on the CSMT, as derived from OCT imaging.

Mild macular edema, defined as CSMT <250 µm, is treated primarily with MPLT, using both focal and grid treatments simultaneously. In selected cases, there may be a need for adjunctive intravitreal anti-VEGF injections.

Moderate macular edema, (CSMT >250 µm and <400 µm), can and will respond well to MPLT initially, but sometimes it is necessary to supplement with pharmacologic therapy. Moderate macular edema is typically treated initially with 2 intravitreal anti-VEGF injections 1 month apart. If there is no significant reduction in CSMT, patients may proceed to MPLT. If there is a response to the initial anti-VEGF injections, I continue for a maximum of 3 additional injections before proceeding to MPLT. I may selectively use an anti-VEGF agent after laser therapy as well.

In severe cases of macular edema, CSMT >400 µm, it is possible to treat exclusively with MPLT, but it will require numerous sessions. Therefore, I typically start with 3 intravitreal anti-VEGF injections 1 month apart. If there is a response to the initial injections, I continue for a maximum of 3 additional injections and then proceed to MPLT, provided that CSMT is <400 µm. If there is insufficient reduction of CSMT, I then consider using an intravitreal corticosteroid analogue such as triamcinolone acetonide or the dexamethasone intravitreal implant (Ozurdex, Allergan, Inc.). After 1 month of the intravitreal corticosteroid analogue administration, I then proceed to MPLT. By initially reducing CSMT to <400 µm, I can achieve a better response without repeating laser treatment as often.

CONCLUSION
The goal of DME therapy is to achieve the greatest reduction in macular thickness, in the shortest amount of time, with the least amount of side effects and with the greatest duration. I am able to achieve that by combining MPLT and pharmacologic VEGF inhibitors.

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