The Role of Focal Laser in the Anti–Vascular Endothelial Growth Factor Era

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ABSTRACT

INTRODUCTION: To review important studies examining focal laser for diabetic macular edema (DME), to examine real-world data regarding actual treatments patients are receiving, to present long-term visual outcomes in real-world practice, and to suggest an evidence-based approach for the use of focal laser.

METHODS: This study is a review of landmark studies evaluating focal laser and pharmacologic therapy for DME. In addition, the authors include a retrospective review of 102 consecutive eyes of 53 patients in our practice setting in rural Alabama. A chart review was performed, and patients were included if they were diagnosed with DME and were treated with both focal laser and bevacizumab. Bevacizumab and focal laser were given on a “as needed basis” at the discretion of one treating physician (J.O.M.). Worse visual acuity or worsening macular edema were indications for additional treatment. Statistical analysis was performed using frequencies and percentages. Best-corrected visual acuity (BCVA) was recorded at baseline and at the end of treatment (mean of 5 years) in the medical record. Primary outcome measures were BCVA, patients with better than 20/40 BCVA, patients with worse than 20/200 BCVA, and patients with stable BCVA.

RESULTS: Anti–vascular endothelial growth factor (VEGF) therapies are the first-line treatment for DME, but real-world claims data suggest that diabetic patients cannot come in for monthly injections as in large clinical trials. In our series, after a mean of 5 lasers and 5.5 injections, 90% of eyes had stable or better BCVA, 65% were ≥20/40, and only 13% were ≤20/200.

CONCLUSIONS: Laser treatment for DME remains an important adjunctive therapy

KEYWORDS: Diabetic macular edema, focal laser, anti-VEGF, diabetic retinopathy, diabetes

Introduction

For decades now, focal laser has been the best treatment available for diabetic macular edema (DME). The retina world, however, has entered a new era: the era of anti-vascular endothelial growth factor (anti-VEGF). There is no question regarding the efficacy of anti–VEGF agents for the treatment of DME. In DRCR.net Protocol I, almost 50% of patients in the ranibizumab group gained 2 lines of vision, whereas in the sham plus laser group, only 28% of patients gained 2 lines.1 In ideal study settings where patients come in for monthly appointments, the clinical trial data clearly suggest that anti–VEGF agents are superior to laser for DME. But what does data actually show in real-world practice settings? How many injections are patients actually getting? How many appointments are these diabetic patients actually making? Does focal laser still have a prominent role in the management of DME? Herein, we review key studies from the past regarding focal laser, we examine current real-world data, including our large retrospective long-term study of 102 consecutive eyes receiving both laser and intravitreal injections, and we consider a practical evidence-based approach to the treatment of DME.

A Look Back at the Past

The landmark study that established focal laser for DME is the Early Treatment of Diabetic Retinopathy Study (ETDRS). In this study, researchers found a 50% reduction in moderate vision loss (defined as retinal doubling of the visual angle or a loss of 3 lines on the ETDRS chart) in patients that underwent focal laser for Clinically Significant Macular Edema (CSME), defined as retinal thickening within 500 μm of the foveal center, hard exudates within 500 μm of the foveal center with associated retinal thickening, or 1 disc area of retinal thickening within 1 disc diameter of the foveal center. Specifically, at 2 and 3 years after laser treatment researchers found a reduction in moderate vision loss from 24% to 12% (year 2) and 33% to 13% (year 3), respectively.2 This included patients with both foveal center-involved DME and non–center-involved DME. Thus, focal laser has been proven effective for both foveal and extrafoveal DME. It is interesting to note that anti–VEGF agents have not been tested in rigorous clinical trials for treatment of extrafoveal DME.3 The ETDRS has clearly established focal laser as an effective treatment for both center-involved and non–center-involved CSME.
Moving Forward: Focal Laser Studies by the DRCR Network

The ETDRS may have established focal laser as an effective treatment for DME, but the multiple large-scale clinical trials performed by the DRCR Network (DRCR.net) has helped clarify (to some degree) the role of focal laser in the anti-VEGF era. What follows is a brief review of important DRCR.net protocols that are relevant to the role of focal laser today.

Protocol A compared modified ETDRS focal laser with “mild macular grid (MMG) laser photocoagulation.” Mild macular grid laser burns are lighter and distributed in a grid pattern throughout the macula in both thickened and nonthickened areas of the retina. Mild macular grid laser does not aim to directly treat microaneurysms. Modified ETDRS focal laser aims to directly treat microaneurysms and treats only areas of thickened retina or capillary nonperfusion. Of note, the ETDRS laser group was termed “modified” because the type of laser used in the study was adjusted from the original ETDRS to reflect current practice. The laser spots were slightly smaller (50 μm), lighter (gray), and a color change was not required when treating the microaneurysms. The DRCR.net researchers found modified ETDRS laser to be better than MMG laser for DME in terms of optical coherence tomography (OCT)-based retinal thickness measures. However, best-corrected visual acuity (BCVA) measures in the 2 groups were not substantially different. Other types of laser modalities, namely, micropulse and subthreshold laser, will be discussed in detail below. In Protocol A, researchers specifically evaluated the effect of modified ETDRS laser on retinal thickening in eyes with non–center-involved DME. Vision was stable, and both retinal thickness and fluorescein angiogram leakage were decreased at 1 year. The study concluded that modified ETDRS focal laser was still an appropriate treatment for extrfoveal DME.

In addition to studies such as Protocol A that compared laser modalities, the DRCR.net has provided studies that compare focal laser with various pharmacologic therapies. Protocol B was one such study that compared intravitreal triamcinolone with focal laser. Both 1 and 4 mg doses were compared with focal laser at 4-month intervals for DME. Focal laser was found to be superior to triamcinolone in terms of visual acuity and OCT thickness. Patients in the triamcinolone group also had a significantly increased risk of cataract and glaucoma. In a similar study, Protocol C compared subtenon triamcinolone with or without adjunctive laser to focal laser alone. Patients in this study had DME and relatively good vision (patients had to see better than 20/40 to be included in the study). At the conclusion of the study, there was no significant difference in vision or retinal thickening, although there was a suggestion of a greater proportion of eyes having a central subfield thickness of less than 250 μm when laser was used in combination with subtenon triamcinolone. Based on this study, subtenon triamcinolone is not recommended as a treatment for DME. One of the most important studies comparing focal laser with pharmacologic modalities was Protocol I. This clinical trial compared focal laser with both ranibizumab with prompt or deferred focal laser and intravitreal triamcinolone plus prompt laser. Prompt laser was defined as within 3 to 10 days of the diagnosis or injection (if the patient was randomized to an injection group). Deferred laser means greater than 6 months after the initial injection. Ranibizumab with prompt or deferred laser was found to be more effective than sham injection plus prompt laser (ie, focal laser alone). As in previous studies, patients in the triamcinolone group were at increased risk of cataract and increased intraocular pressure. Of note, in pseudophakic eyes, triamcinolone plus prompt laser was clearly superior to laser alone. In another analysis from Protocol I, researchers specifically evaluated different wavelengths of laser (namely, yellow and green laser). This study suggested that there were not likely any large clinical differences between green and yellow laser. Protocol K was another study with important implications regarding the durability of focal laser. In this study, eyes with center-involved DME were treated with focal laser. Of the eyes that showed a definite reduction in retinal thickening at 4 months after laser, 23% to 63% of these eyes showed continued improvement without additional treatment. Protocol K demonstrated a slow improvement in DME with focal laser that may continue to improve even after 4 months from the initial treatment, suggesting a degree of durability with focal laser. Protocol T was a landmark study designed to compare the 3 anti-VEGF medications: bevacizumab, ranibizumab, and aflibercept. Most ophthalmologists are aware that aflibercept was found to be superior to avastin and ranibizumab for DME in eyes with 20/50 or worse vision. Although the absolute difference in visual acuity between aflibercept and the other medications narrowed in terms of statistical significance at 2 years, the so-called “area under the curve” suggested a statistically significant difference cumulatively over the course of the 2 years of the study. It is also interesting to note that during the study, each group was allowed rescue focal laser after 6 months of treatment for persistent DME. In fact, 37% of aflibercept patients, 56% of bevacizumab patients, and 46% of ranibizumab patients needed laser from weeks 24 to 48 during the study. This suggests that even in study conditions where follow-up is carefully monitored and patients are coming in every month, patients still may require focal laser.

Beyond the DRCR Network: Other Important Studies

A number of other studies of patients with DME that have compared anti-VEGF agents and focal laser deserve mention as well. The Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT) study compared bevacizumab and focal laser. About 32% of bevacizumab-treated eyes gained greater than 3 lines of vision, whereas only 4% of eyes in the laser group gained 3 lines. In the Ranibizumab for Edema of the MACula in Diabetes (READ) 2 study, researchers...
focused on ranibizumab versus focal laser. Over the course of the first 6 months, ranibizumab alone was compared with laser alone as well as ranibizumab combined with laser. After 6 months, ranibizumab and ranibizumab plus laser were found to be superior to laser alone. Over the next 2 years, the laser-alone group was allowed to receive ranibizumab, and by the end of 2 years, the laser group had caught up to the other groups in terms of vision. Researchers concluded that ranibizumab was certainly effective for DME. Also, when ranibizumab was used in combination with laser, the amount of residual edema was reduced as were the number of injections.13 This is an important point socially and economically for the diabetic patient population, as will be discussed further below. Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema (RESTORE) was another important clinical trial that similarly compared ranibizumab and ranibizumab plus laser with laser alone. In both the ranibizumab group and the combination group, 22% of patients gained 3 lines of vision, whereas only 8% in the laser-alone group gained 3 lines of vision.14 Three other studies that should be mentioned included RESOLVE, RISE, and RIDE. In Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE), ranibizumab was found to be superior to sham injections. RISE and RIDE demonstrated ranibizumab’s superiority to laser.15–16 In short, the data overwhelmingly have established anti-VEGF to be the first-line treatment for DME, but many of the studies also suggest a continued role for focal laser (see Table 1). Before the role for focal laser in today’s world is more fully discussed, one other topic should be mentioned: micropulse/subthreshold laser.

### Micropulse/Subthreshold Laser: An Emerging Modality?

The use of modified ETDRS focal laser to create light burns on the retina to reduce DME has been discussed thus far. Although less studied, the emerging modality of micropulse and subthreshold laser treatment for DME certainly deserves mention. The idea is simple. Even modified ETDRS laser is a photodestructive procedure, micropulse/subthreshold laser uses short pulses of laser to treat the retina in such a way that there is no visible retinal burn and theoretically less retinal destruction. Because the term “sub-threshold” has been used in many different ways, some definitions are in order. Classical subthreshold laser involves use of conventional lasers (continuous wave argon, krypton, and diode lasers) to treat the retina in a “gentler” way. Basically, this is a modified ETDRS laser with a very light burn. Clinical subthreshold is a laser that cannot be seen bimicroscopically. This type of laser involves the use of micropulsed lasers (10-30 ms) to create an invisible burn. The end goal is still laser-induced damage which, although not visible at the slit lamp, can be seen with autofluorescence, OCT, etc. Finally, true subthreshold laser is a micropulsed laser that results in no detectable burn even by current multimodal imaging.17

Terminology aside, the important question is this: does true subthreshold laser work? In a prospective randomized trial, Figueira et al18 compared modified ETDRS laser in 40 eyes with subthreshold micropulse diode laser in 44 eyes. The researchers found no difference in visual acuity or OCT thickness.18 Moreover, a recent meta-analysis of 7 randomized controlled trials showed similar outcomes between modified

### Table 1. Summary of key DME studies involving focal laser therapy.

| STUDY                  | KEY FINDING                                                                 |
|------------------------|-----------------------------------------------------------------------------|
| ETDRS                  | 50% reduction in moderate vision loss with focal laser, 17% gain 1 line; of those able to gain 3 lines, 40% did so |
| DRCR.net Protocol A    | Modified ETDRS laser better than modified macular grid laser for DME         |
| DRCR.net Protocol B    | Modified ETDRS focal laser superior to intravitreal triamcinolone           |
| DRCR.net Protocol I    | Ranibizumab plus laser is more effective than laser alone, triamcinolone is superior to laser in pseudophakic eyes, 28% of focal laser-alone groups still gained 2 lines of vision |
| DRCR.net Protocol K    | 20%-60% of eyes that initially respond to focal laser may continue to improve after 4 months, suggesting durability of effect |
| DRCR.net Protocol T    | Aflibercept is superior to bevacizumab and ranibizumab for DME in eyes with 20/50 or worse vision. Approximately 50% of eyes still required rescue focal laser |
| BOLT study             | Bevacizumab is superior to focal laser alone                                |
| READ 2 study           | Ranibizumab and ranibizumab with laser are superior to focal laser alone. Using laser with ranibizumab may decrease the number of injections required to control DME |
| RESTORE                | Ranibizumab and ranibizumab with laser are superior to focal laser alone     |
| RISE and RIDE          | Ranibizumab is superior to focal laser                                      |

Abbreviations: DME, diabetic macular edema; ETDRS, Early Treatment of Diabetic Retinopathy Study; RISE and RIDE, A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus.

*All drugs referred to above were given intravitreally.*
ETDRS laser and subthreshold laser. Two of the trials suggested that subthreshold causes less retinal damage.\textsuperscript{19} Although this emerging laser modality is less studied, the early data suggest that true subthreshold laser may have an important role in the treatment of DME without causing as much collateral retinal damage as ETDRS laser.

**Real-World Data**

It is clear from the studies summarized above that anti–VEGF agents are the preferred and most effective treatment for DME. In ideal study conditions where patients are able to maintain close monthly follow-up for injections, anti–VEGF agents clearly outperform laser. But does real-world practice mirror DRCR network study conditions?

Diabetes is a challenging condition for patients for many reasons. The retina specialist is well acquainted with the microvasculopathy affecting the eye, but these patients also have neuropathy, nephropathy, and other end organ–related damage from the disease. As such, diabetic patients have many appointments with primary care providers and other specialists every month. Many patients are on dialysis 3 times a week. Without a doubt, it is a significant additional burden both socially and economically for these patients to visit the retina specialist every month! In addition, consider the fact that many diabetics are young, have jobs, and may be the sole wage earner for their family, and it becomes clear that some appointments will be missed.

So how often are these patients missing appointments? Studies show a range of missed appointment rates, but some rates approach 40%.\textsuperscript{20} Surely these rates vary across different social circumstances, but regardless, this high rate of no-shows for diabetic patients can result in poor blood sugar control, more emergency room visits, and relevant to the current discussion, missed injection appointments. In DRCR.net Protocol I, patients received 8 to 9 injections in the first year,\textsuperscript{8} and in DRCR.net Protocol T, patients received 15–16 injections over 2 years.\textsuperscript{11} Similarly, the RISE/RIDE study patients underwent monthly injections.\textsuperscript{16} In contrast, a claims analysis revealed that patients with newly diagnosed DME were actually receiving between 2.2 and 3.6 injections per year. In addition, only 31.2% of patients with newly diagnosed DME actually received 3 or more injections in the first 4 months after diagnosis.\textsuperscript{21} There is a huge discrepancy between the number of injections patients in the real world are actually getting and the number of injections patients in the large clinical trials are getting.\textsuperscript{22}

There are 2 reasons for this discrepancy, the first having been alluded to in the previous discussion. Namely, it is a significant burden for diabetics to come in for monthly injections. Their numerous visits to primary care doctors and other specialists, their social situation, and life in general make it inevitable that some appointments with be missed. The second reason is that many retina specialists recognize that focal laser still works and continue to apply it additionally to patients in the real world.

**Real-World Retrospective Long-Term DME Treatment Study**

Given the real-world claims data and the recognition that many retina specialists still consider focal laser an important adjunct in the management of DME, we present some additional data from our real-world practice setting. In our private practice in Alabama with a university affiliation, after Institutional Review Board approval, we conducted a retrospective study in which 53 consecutive patients (102 eyes) diagnosed with DME were treated with both focal grid laser and intravitreal bevacizumab over a mean of 5 (range: 1–20) years and examined to assess visual acuity before and years after treatment. Best-corrected visual acuity, patients with ≥20/40, patients with ≤20/200, and patients with stable vision following treatment were the primary outcome measures. Secondary outcomes were numbers of lasers and intravitreal injections given and their correlation with final vision.

A total of 102 eyes were examined in 53 patients. Mean age of the patients was 64 (range: 36–91) years. In total, 28 men (53%) and 25 women (47%) were treated. Of 53 patients, 30 were white (57%) and 23 were African American (43%). The mean length of time patients had been diagnosed with diabetes mellitus was 22 (range: 4–53) years. Mean follow-up time from the beginning of treatment was 5 (range: 1–20) years. Of 53 patients, 4 (8%) had one eye treated, whereas 49 (92%) had both eyes treated. Patients received on average 5 lasers (range: 1–19) and 5.5 injections (range: 1–25). Following treatment, 92/102 eyes (90%) examined had stable or improved vision, whereas 10/102 eyes (9.8%) had worsened vision. Mean pretreatment visual acuity was 20/100 and mean posttreatment visual acuity was 20/80. Final visual acuity was ≥20/40 in 66/102 cases (65%). In these cases, patients received on average 5.5 lasers and 5 injections. Resultant visual acuity was ≤20/200 in 13/102 cases (13%). In these cases, patients received an average of 4.5 lasers and 6.7 injections. There was no correlation between visual acuity and number of lasers and intravitreal injections at all final visual acuity levels (P = 1.0).

The findings of our study demonstrate the efficacy of focal grid laser with minimal intravitreal anti–VEGF injections resulting in stabilization of visual acuity in most of the patients, as well as most of the patients maintaining ≥20/40 visual acuity over a mean 5-year treatment period. Our mean pretreatment visual acuity of 20/100 was probably lower than most previous studies, secondary to the following: poor compliance, lower socioeconomic status, 17% of patients with transportation issues, 40% on disability, 45% with only a high school education, and 75% unemployed, all consistent with rural health care in the state of Alabama. Nevertheless, most of our patients undergoing long-term treatment for DME remained stable or improved. We also found the number of intravitreal injections...
to be drastically reduced from prior clinical studies including the RISE/RIDE, BOLT, and DRCR Protocol I and Protocol T studies.8,11,12,16 We believe that the number of lasers in our study was much higher than the number of lasers given in previous clinical trials involving intravitreal injections. We postulate that these increased numbers of focal grid lasers contributed to the necessity for less intravitreal injections, all resulting in stable or improved vision in most of our patients. These data suggest that long-term follow-up of eyes treated for DME with almost equivalent numbers of focal grid laser and intravitreal bevacizumab is effective for maintaining visual stability, improving visual acuity in most of the patients and resulting in very few patients with poor visual acuity. This is more objective data coming from the real-world practice setting that suggests that focal laser treatment is certainly a useful adjunctive treatment for DME. In our series, not only did patients maintain good vision, but they also received a much more realistic number of injections, similar to Medicare claim rates of intravitreal injections, in contrast to the major clinical trials of anti-VEGF (once monthly).

Real-World Treatment of DME: The Role of Focal Laser

The ETDRS is the landmark study previously discussed that clearly demonstrated the benefit of focal laser for DME. In addition to the 50% reduction in moderate vision loss mentioned above, 17% of eyes in this study gained greater than 1 line of vision, and of those able to gain 3 lines of vision, 40% did so.2 Moreover, we have also seen how 28% of patients in the DRCR.net Protocol I focal laser plus sham group gained at least 2 lines of vision.8 Our retrospective analysis also suggests that focal laser in the long-term real-world practice setting is effective in maintaining visual acuity better than 20/40 in 65% of cases. Clearly, focal laser for DME is an established and effective treatment option for patients with DME. In addition, these patients can be treated in one office visit or at least in fewer office visits if concomitant use of anti-VEGF is considered. From a cost standpoint, 1 session of focal laser is substantially cheaper than monthly injections over the course of 1 to 2 years. Less office visits with fewer injections also means fewer opportunities for causing postinjection endophthalmitis over time. Less injections over time also means fewer opportunities for causing injection-associated uveitis, postinjection pain, and transient blurry vision after injections. In a recent survey study evaluating patient preferences for DME treatment with focal laser versus injections, the authors found that most patients found focal laser treatment easier than injections, although there was not a statistically significant difference in patient preferences between the 2 treatment modalities.25 Given the claims data that suggest patients are only receiving 2 to 3 injections per year, the authors suggest that focal laser remains an evidence-based, reasonable, economical, and effective treatment for DME today.

As with many problems in medicine, the real-world approach to DME requires an individualized approach based on each patient’s situation. In certain scenarios, monthly injections following the large-scale clinical trials may be best for the patient, and the study data clearly show the effectiveness of such an approach when close follow-up can be maintained. In many real-world situations, however, we suggest a modified approach that can control a patient’s DME with a more reasonable number of office visits. After all, what benefit is there if a patient gets 2 monthly injections and then comes back a year later? Instead, why not treat a patient with several injections and then consider focal laser and allow the patient several months before the next visit. This patient may require additional injections and/or laser in the future, but the number of office visits will be reduced and the DME will be controlled with less of a burden to the patient and clinic. Such a treatment paradigm may not require additional injections in some cases after the initial focal laser treatment. Moreover, if this patient were to miss several visits due to unforeseen circumstances (hospitalization, job-related issues, noncompliance, etc), there is a better chance that the DME will be under better control due to the longer duration and more permanent effect of focal laser. Furthermore, in certain cases with non–center-involved DME with obvious microaneurysms as the source of leakage, focal laser can be considered as a primary treatment. Such a treatment approach may control the DME with 1 treatment session. Then, when the patient returns a year later having been lost to follow-up (as may often be the case in this patient population), the patient will not have severe vision loss from severely worsened DME.

Conclusions

The large discrepancy between the number of injections given in large-scale clinical trials and real-world practice is because of poor patient follow-up inherent in the diabetic population and because many retina specialists recognize that focal laser remains an important adjunctive tool for treatment of DME. Focal laser for DME is not dead. In fact, it remains as a practical, effective, evidence-based, and cost-effective approach for patients with DME that offers the most when used in conjunction with injections and in many cases reducing the injection burden for these patients.

Author Contributions

JOM, JNC, and LM conceived and designed the experiments; analyzed the data; contributed to the writing of the manuscript; agree with manuscript results and conclusions; jointly developed the structure and arguments for the paper; made critical revisions and approved final version; and wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript.

Disclosures and Ethics

As a requirement of publication, author(s) have provided to the publisher signed confirmation of compliance with legal and
ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material.

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