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Multiple Laser Photocoagulation Treatments for the Management of Diabetic Macular Edema

Sadhna Vora

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Sadhna Raju Vora

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ABSTRACT

MULTIPLE LASER PHOTOCOAGULATION TREATMENTS FOR THE MANAGEMENT OF DIABETIC MACULAR EDEMA

Sadhna Vora, Curtis Hagedorn, Ron Adelman.

Department of Ophthalmology, Yale University School of Medicine, New Haven, CT.

The purpose of this study was to evaluate functional and funduscopic outcomes amongst patients receiving multiple treatments with macular laser photocoagulation for clinically significant diabetic macular edema. A record review was conducted of patients who had multiple macular laser treatments for diabetic macular edema. As part of routine follow-up for diabetic macular edema, visual acuity and funduscopic findings were assessed before a given laser treatment and at 6 months afterwards. The study included 64 eyes from 41 patients. There was no statistically significant difference between the proportion of eyes that showed funduscopic improvement after treatment 1 versus the proportion of eyes that improved after subsequent treatments. For the first laser treatment, 44 of the 64 eyes (69%) showed funduscopic improvement in edema. 35/64 (55%) of eyes showed improvement after the second treatment ($p=0.15$); 29/40 (72.5%) eyes showed improvement after the third treatment ($p=0.85$); 15/18 (83.3%) eyes showed improvement after treatments ≥ 4 ($p=0.36$). Similarly, in terms of visual acuity outcomes, there was no statistically significant difference between the proportion of eyes with preserved visual acuities after treatment 1 compared to repeat treatments. This study found that the majority of eyes that receive re-treatment after initial laser therapy will respond with an improvement in macular edema.

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INTRODUCTION

Diabetes is one of the leading causes of new blindness in the United States, giving rise to ocular microvascular complications such as diabetic retinopathy and diabetic macular edema. Diabetic retinopathy is the proliferation of new blood vessels secondary to ischemia of the retina. These new blood vessels are fragile, prone towards hyperpermeability and microaneurysm formation. Leakage through these vessels causes a breakdown of the blood-retinal barrier with subsequent retinal thickening, a process that gives rise to diabetic macular edema. Currently, tight glycemic control is the primary method of prevention of this long-term complication of diabetes. Treatments for advanced stages of the condition include laser photocoagulation and intra-ocular steroid injection.

Epidemiology

Diabetic retinopathy is one of the major causes of blindness in the U.S. in adults between the ages of 20 and 74, accounting for 8% of all cases of legal blindness and 12% of new diagnoses of blindness each year (1). It has been shown that the duration of hyperglycemia, in addition to its extent, correlate with the severity of retinopathy (2). Clinically significant macular edema (CSME) is one of the complications of retinopathy that is potentially vision threatening in both type 1 and type 2 diabetics. The incidence of CSME after 10 years of follow-up has been estimated at approximately 20% in Type I diabetics, 25% in Type II insulin dependent diabetics, and 13.9% in type II non-insulin

dependent diabetics (3). Approximately half of patients with CSME will lose two or more lines of VA within 2 years (4).

Diabetes-related blindness and visual impairment places significant demands on society, both monetarily and in terms of quality of life. The cost of blindness to the federal government was found to be over $4 billion dollars in 1990 according to one study, with 97% of this expenditure devoted to working age adults (5). This value accounts for both direct costs such as medical and personal care and the indirect cost of loss of labor. More difficult to quantify is the effect on quality of life endured by patients with diabetes related vision problems (6). In a recent study of 95 patients with diabetic retinopathy, 64 of 95 patients were willing to trade time of life in return for perfect vision in both eyes. The average patient expected to live for an additional 15.6 years and was willing to trade 3.3 of those remaining years in return for perfect vision (7).

Pathophysiology

Diabetic retinopathy follows an orderly progression. It begins as mild, nonproliferative changes that include increased vascular permeability. It proceeds to moderate-to-severe nonproliferative retinopathy, characterized by microaneurysms and hemorrages. This is the stage that macular edema is observed. Finally, there is a progression to proliferative diabetic retinopathy, in which fragile new blood vessels proliferate. Several studies have shown that hypertension and poor glycemic control contribute to the development of diabetic retinopathy and macular edema. The biological

pathway of these changes is not fully understood, although several potential mechanisms have been proposed.

Blood vessel walls do not need insulin to allow movement of glucose into cells. Therefore the high levels of glucose present in diabetes allow for a greater than normal influx of glucose into cells of capillaries. The glucose then gets metabolized to sorbitol, a molecule too large to diffuse back out of the cells. Osmotic flow of fluid into the cell results from the accumulation of sorbitol, ultimately leading to damage of endothelial cells and pericytes (8, 9). The result is weakening of capillary walls and subsequent microaneurysm formation. The thickening of the capillary basement membrane and increased deposition of extracellular matrix proteins interfere with the autoregulation of retinal blood flow, further contributing to microaneurysm formation. Leakage from these microaneurysms causes macular edema.

In addition to the alteration of hemodynamics as a potential cause of diabetic macular edema, the increased leukocytosis that has been observed in diabetes has been implicated as another potential contributor. Leukocytes adhere to vascular endothelium, altering blood flow. In addition, superoxides and proteolytic enzymes generated by leukocytes have been proposed to damage vascular endothelium and limit capillary perfusion (10). Supporting this theory is the observation that capillary leakage is associated with increased retinal white blood cells in diabetic laboratory rats (11).

There are two types of CSME, focal and diffuse, which differ both in their pathophysiology and appearance. Focal lesions are the result of local microaneurysm formation. Diffuse macular edema, by contrast, is caused by widespread vasodilation of the retinal vasculature as the result of the retinal nonperfusion in diabetes (11).

Diagnosis:

CSME is defined by any one of the following: A) any retinal thickening at or within 500 micrometers of the center of the macula B) hard exudates at or within 500 micrometers of the center of the macula if associated with an adjacent area of thickening and/or C) a zone or zones of thickening one disc area in size or larger, any part of which is within one disc diameter of the center of the macula (12) (*See Figure 1*). It is important to note that vision loss is most threatened when CSME involves the center of the fovea.

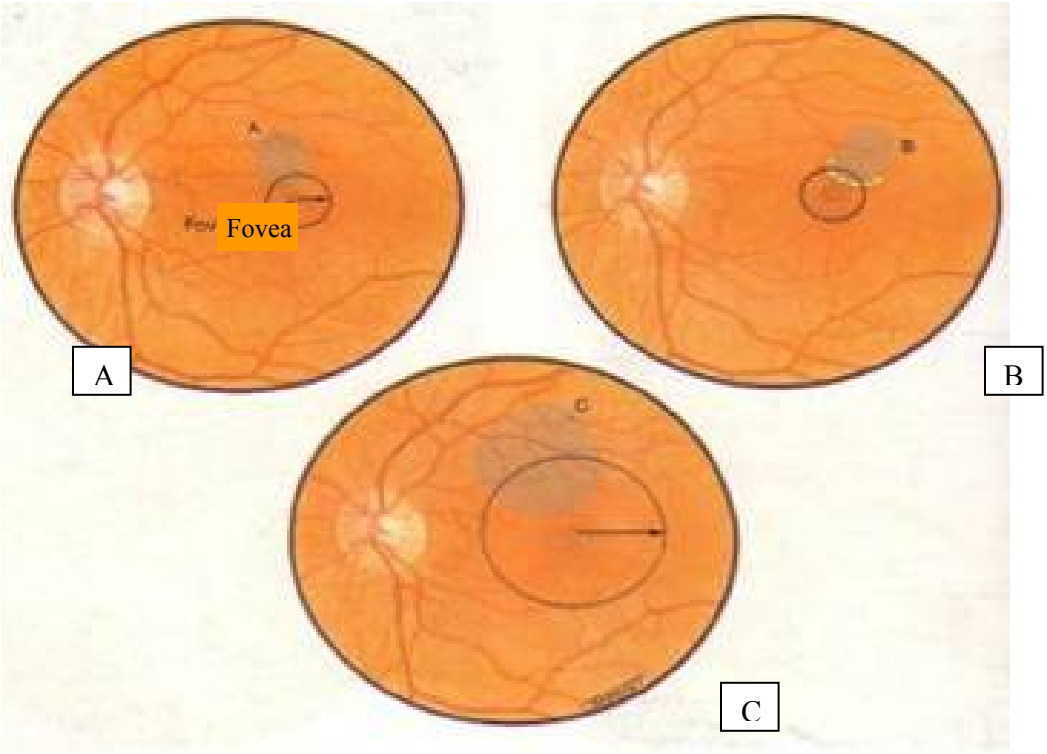

Figure 1: Clinically Significant Macular Edema: CSME is defined as at least one of the following: A) Retinal thickening within 500 micrometers of center of the macula B) hard exudates at or within 500 micrometers of the center associated with thickening and/ or C) a zone or zones of thickening one disc area in size or larger, any part of which is within one disc diameter of the center of the macula.
Image courtesy of medindia.net

Early detection is crucial for the management of CSME. Current treatment strategies are effective at curbing the progression of vision loss but are not successful at restoring visual function that has already been compromised (13).

Currently, the standard means of detecting diabetic macular edema, and one of the methods that was employed in this study, is the presence or absence of macular thickening on fundoscopy. This method is complementary with fundus photography, in which standard seven-field stereoscopic-color fundus photographs are obtained through a dilated pupil (14, 15).

Other methods of detection include fluoroscein angiography. Patients are given an IV or oral load of fluorescein, which normally cannot pass through the blood-retina barrier. However in certain disease states such as diabetic retinopathy, fluoroscein can traverse across hyperpermeable capillary walls, and can be visualized as "leakage". This method is more sensitive at detecting capillary leakage than funduscopy or fundus photography. In addition, it also allows for detection of nonperfusion of the retina. Fluorescein angiography is especially useful when the decision to perform laser photocoagulation treatment has already been made, as it allows for determination of problem areas (11).

Finally, the newest technique for detection of CSME is ocular coherence tomography, or retinal thickness analysis. This is a quantitative measure of CSME, unlike the other methods of detection. This technique operates on similar principles as ultrasound, but uses light waves instead of sound waves to detect ocular structures, allowing for a much higher resolution of images (approximately 10 microns). A standard 200 watt 830 nm ray of light is split by an interferometer into a probe light beam and a

reference light beam. The probe beam is pointed into the eye and the amount of time it takes to reflect back allows for a determination of the structural features of the retina. Multiple scans are taken and combined into a tomogram, which provides a 2-D representation of the back of the eye (16).

In 1998, Hee et al. designed a standard OCT protocol to measure diabetic macular edema. In their protocol, six OCT scans are taken radially with fovea as center. Then the retinal thickness is calculated at 600 macular locations. These calculations allow for the production of a map of the topography of the eye (17).

The benefits of OCT include its high sensitivity for CSME, the ease of its use, its non-invasive nature, and the reproducibility of the results. This last aspect allows for ease of monitoring the changes in a patient's condition over time. Furthermore, an important advantage over fluorescein angiography stems from the fact that substantial vision loss associated with macular thickening can occur in the absence of fluorescein leakage.

Treatments:

Control of the metabolic effects of diabetes has been shown to have a strongly positive influence on the microvascular complications of the disease. The United Kingdom Prospective Diabetes Study (UKPDS) showed that glycemic control in type 2 diabetics led to a 21% reduction in the risk of progression of retinopathy over roughly a decade (18). Furthermore, treatment of hypertension in this patient population with either a beta blocker or an ACE inhibitor decreased the progression of diabetic retinopathy by

34% and was associated with a reduction in vision loss of close to 50% over the 7.5 year study period (19).

Once CSME macular edema has been diagnosed, treatment options include laser photocoagulation treatments as well as medical therapies. In more severe cases, surgical therapy is of benefit. In such cases, vitreal traction is observed, owing to the development of a thin membrane over the retina. Removal of the membrane reduces traction and has been associated with improvement in CSME. Finally, newer pharmacological treatments include the use of PKC inhibitors and intravitreal triamcinolone injections. The basis for the use of the former is evidence that the hyperglycemia of uncontrolled diabetes induces the synthesis of diacylglycerol, which in turn activates protein kinase C (PKC). PKC B, in particular, induces retinal microvascular changes leading to increased permeability (20) and altered blood flow (21). PKC inhibitors prevent this process, thereby curbing macular edema formation.

The use of intravitreal triamcinolone injection is based on the reduction of inflammation caused by corticosteroids, as well as their observed downregulation of the production of VEGF (22) and protection of the blood-retinal barrier (23). Notably, intraretinal injection of corticosteroids has been shown to be effective in patients for whom laser photocoagulation has failed (24). However, the long term efficacy of intraretinal steroids has been called into question (25), suggesting that repeated injections might be necessary for the stabilization of visual acuity.

Furthermore, triamcinolone injection can cause several important complications. Notably, intravitreal triamcinolone (IVT) has been associated with glaucoma in roughly 35-50% of patients (24, 26-27). Furthermore, Challa et al. found progression of cataracts

in 6 of 26 patients (23%) after 1 treatment with triamcinolone injection (28). Similarly, Jonas et al. reported that 20% of 71 patients underwent cataract removal surgery within 6 months of IVT (29). Finally, endophthalmitis has been found to be a rare complication of this form of treatment, with a prevalence of 0.3% per injection and 0.9% per eye (including cases of noninfectious endophthalmitis). Excluding cases reported specifically as noninfectious endophthalmitis, the prevalence of endophthalmitis was 0.2% per injection and 0.5% per eye. (30)

Given that the treatment method employed in this study was laser photocoagulation, we will discuss it in greater depth at this time. The defining study in regards to the management of diabetic macular edema is the EDTRS study, which involved 3928 patients in multiple study centers from 1979 to 1989. A significant result of the ETDRS was the definition of CSME, which was discussed above. The results of the ETDRS demonstrated that focal/grid laser treatment for CSME reduced the risk of moderate visual loss by up to 50% over a three year period (12, 31, 32). Supporting the success of laser photocoagulation treatments was the observation also that CSME resolved in up to 92% of cases treated by laser photocoagulation (33). However, while many eyes showed promising results with laser treatment, a substantial cohort did not. According to ETDRS, 12% of treated eyes still lost at least 15 ETDRS at the three-year point. Furthermore, almost 25% of eyes had thickening of the fovea at three years.

The mechanism of action of macular laser for CSME is not clear. In this treatment method, laser is applied directly to areas of leaky microaneurysms and in a grid pattern in areas of diffuse macular edema (34). Early theories described acute closure of leaking microaneurysms by immediate “whitening” or “darkening” of microaneurysms

upon application of laser (12). The likely mechanism for closure is likely thermocoagulation induced by laser treatment. Subsequent clinicopathological study has demonstrated that these microaneuryms may close after clinically weak burns (35, 36), and closure may be delayed up to 12 weeks (37), suggesting an indirect mechanism. This theory of an indirect mechanism has been further strengthened by the findings of success with laser using longer wavelengths (38-40).

Resolution of macular edema after laser photocoagulation is a gradual process, occuring on a time scale of several months. First, the fluid associated with CSME is absorbed across the blood retinal barrier, occurring between 3 and 6 months after laser treatment (11). During this time period, lipoproteins dissolved in the edema fluid may precipitate out, forming hard exudates. It is important to note that the diabetic retinopathy/ edema may appear to be worsening during this stage. The lipoproteins are later digested by macrophages in the eye. Only after the completion of this process does macular edema resolve.

STATEMENT OF PURPOSE

Several large multicenter studies have shown that laser photocoagulation treatment reduces the occurrence of macular edema in the majority of patients and inhibits progression of vision loss in roughly half of patients. However, there is limited information available regarding efficacy of macular laser retreatments for CSME in those patients for whom the first treatment did not lead to lasting resolution of edema. This question is especially important to answer given the growing popularity and success of alternative treatments for CSME including intravitreal triamcinolone acetonide, PKC inhibitors and vitrectomy surgery (24, 29, 41-46). Given these alternatives to laser photocoagulation, which currently remains the gold standard, it is valuable to assess the efficacy of repeated macular laser treatments.

Our study had two purposes: the first was to examine both visual and funduscopic outcomes in patients receiving two, three, or four or more macular laser treatments. The second goal of this study was to determine whether success or failure after early treatments predicts in any way the success of future laser photocoagulation treatment. In particular, we wished to examine whether complete resolution after a given treatment is associated with a higher rate of success on retreatment (in which case retreatment is given due to a recurrence of edema vs. failure of treatment). In addition, we sought to determine whether there existed a specific number of treatment failures beyond which it became unlikely that retreatment would be successful: in other words, if a patient had experienced poor outcomes after a specific number of consecutive macular photocoagulation treatments, it would not be worthwhile to offer re-treatment with laser photocoagulation.

PATIENTS AND METHODS

Patients who were evaluated at the Yale Eye Center between January, 1988 and May, 2004 for multiple treatments with laser photocoagulation for diabetic macular edema were included in this retrospective record review. Data extracted from the medical records included patients' age, sex, type of laser treatment, visual acuity before treatment and at follow-up, retinopathy changes, and treatment complications. Information about metabolic control and blood pressure were not uniformly available for all of the patients enrolled in this study.

Patients were included based on the criteria for clinically significant macular edema according to the ETDRS. Specifically, the exclusion criteria for the current study included treatment with panretinal photocoagulation, retinal detachment or retinal trauma, prior laser photocoagulation treatment at another institution, visual acuity worse than 20/200 prior to any laser photocoagulation treatments, or concurrent alternate treatment for diabetic macular edema such as triamcinolone acetonide injections or protein kinase C inhibitor before or during the period of treatment. Furthermore, to be included in the present study, patients must have received at least 2 laser photocoagulation treatments and had follow-up evaluations for at least 6 months following their most recent photocoagulation treatment.

Patients in the study received multiple focal/grid laser photocoagulation treatments for diabetic macular edema based on clinical evaluation of their persistent or recurring macular edema.

As part of routine treatment for diabetic macular edema, all patients underwent ophthalmologic evaluation prior to each treatment and at 3 months, 6 months, and 1 year as clinically indicated. In addition, retinal evaluation included stereoscopic fundus examination using the 78 or 90 diopter lens or the contact lens evaluation. Macular edema was described after a given laser treatment as "resolved," "improved," "stable", or "worsened" relative to the pre-treatment exam. In addition, fluorescein angiographs were obtained as clinically indicated.

Laser photocoagulation was conducted in a focal/grid pattern under topical anesthesia. Focal laser was applied to leaking microaneurysms and a grid pattern was used in areas of diffuse edema as described by the ETDRS (47). A macular contact lens and an argon laser were used. Laser applications were given with spot sizes of 50-100 microns for 0.05-0.1 seconds. The power of the laser was adjusted based on thickness of the retina and take of the laser.

The visual acuities and funduscopic findings at the 6 month check-up were used in the present analysis. Fundus findings were determined by comparing stereoscopic funduscopic photos, fluorescein angiographs, and the examining physician notes in the chart.

In the current study a "positive funduscopic" outcome is defined either as complete resolution *or* improvement of diabetic macular edema. "Negative funduscopic" outcomes are identified as either stability or worsening of edema. By contrast, a "positive visual acuity outcome" is defined as either improvement *or* stability of visual acuity as measured by the Snellen logarithmic scale. "Negative visual acuity outcomes" are defined as worsening of visual acuity.

Comparisons of treatment outcomes were done with change in each eye using student t tests for visual acuity and Chi-square or Fisher exact tests for funduscopic changes, as appropriate. This study was approved by the Human Investigations Committee at Yale University School of Medicine.

RESULTS

The study included 64 eyes of 41 patients. *(See Table 1 for the number of patients and number of eyes receiving a given number of laser treatments.).*

	Number of Patients	Number of Eyes
Treatment #		
1	41	64
2	41	64
3	28	40
4+	14	18

Table 1: Number of Patients and Eyes Receiving a Given Number of Treatments. To be included in this study, patients must have had at least 2 laser photocoagulation treatments for diabetic macular edema.

The average visual acuity eyes before treatment was 0.27 logMAR or 0.54 by decimal notation (approximately 20/40 according to Snellen visual acuity notation).

Comparison of Funduscopic Findings for each Treatment

Following the first laser treatment, 44 of the 64 eyes (69%) showed funduscopic improvement in edema, 13 (20.3%) were stable, and 7 (10.9%) showed worsening. The proportion of eyes that showed reduced amounts of macular edema after repeated laser treatment was not significantly different from the results observed after this first laser treatment. Following the second treatment, 35 of 64 (55%) eyes improved, 20 (31.2%) were stable, and 9 (14.1%) worsened (p value for positive outcome of treatment 2 vs. treatment 1 = 0.15). For the third treatment 29 of 40 eyes (72.5%) improved, 8 (19.5%) were stable, and 3 (7.3%) worsened (p value for treatment 3 vs. treatment 1= 0.85). For

≥ 4 treatments, 15 of 18 (83.3%) eyes improved, 1 (5.6%) was stable, and 2 (11.1%) worsened (p value for treatment 4-7 vs.1 = 0.36). (*See Figure 2 for a summary of the funduscopic outcomes after each laser treatment.*)

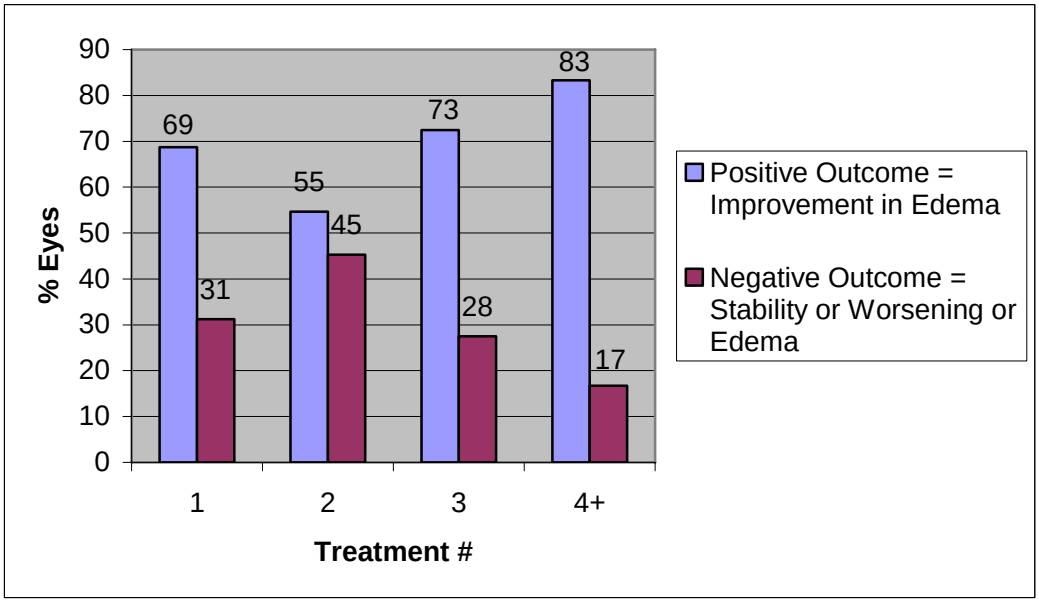

Figure 2: Percentage of Eyes with Positive and Negative Funduscopic Findings for each Treatment. In this figure, positive outcomes are defined as reduction in the amount of macular edema 6 months after treatment. Negative outcomes are defined as stability or worsening of macular edema 6 months after treatment. There is no significant difference between the success rate of the first treatment and that of subsequent treatments.

Furthermore, the proportion of eyes achieving complete resolution after any given repeat treatment was not significantly different from the corresponding proportion after the first treatment. 17 of 64 eyes (26.6%) had complete resolution of diabetic macular edema after the first laser treatment. 14 of 64 eyes (21.9%) of eyes had resolution of macular edema after the second laser treatment (p=0.72 for treatment 2 vs. treatment 1). Macular edema in 16 of 40 eyes (40%) resolved after the third laser treatment (p=0.22 for

treatment 3 vs. treatment 1) and in 7 of 18 eyes (38.9%) after the fourth laser treatment (p= 0.47 for treatments ≥4 vs. treatment 1).

Funduscopic Outcomes of Early Treatments as Predictors of Outcome after Repeated Laser Treatment:

The next goal of the study was to determine whether those patients that had the best results after a given treatment, i.e. complete resolution of edema, had better outcomes upon subsequent treatment than the remainder of patients. To address this question, we conducted analyses to see whether resolution of edema after a given laser treatment predisposed the patient to a better outcome on the subsequent treatment as compared to patients receiving repeat treatments for lack of resolution of macular edema. Retreatment in patients who had achieved resolution of edema after a given treatment was conducted due to recurrence of edema rather than treatment failure.

Based on inclusion criteria, all 44 patients that showed improvement after the first laser treatment required repeat laser treatment, regardless of whether laser treatment had yielded temporary resolution or not. The eyes that had complete resolution of edema after the first treatment had a significantly higher success rate after the second treatment than the remainder of eyes. Of the 17 eyes that had resolution of macular edema after the first treatment and experienced recurrence, 76.5% (n=13) had positive funduscopic outcomes after the second treatment versus 46.8% (22 of 47) of those patients that had not achieved complete resolution after treatment 1 (p=0.048).

Eyes that achieved complete resolution of edema after treatments 2 or 3 showed a trend, albeit not a statistically significant difference, towards better outcomes upon retreatment than their counterparts who had not achieved complete resolution. Of the 40 eyes that needed a third treatment, 9 had achieved complete resolution of edema after treatment 2; 31 eyes had either worsened or not shown complete resolution after treatment 2. 8 of the 9 eyes (88.9%) in the former group had positive outcomes after the third treatment versus 21 of the remaining 31 eyes (67.7%) (p= 0.40.)

Of the 18 eyes that needed a fourth treatment, 6 had achieved complete resolution of edema after treatment 3. All 6 of these eyes (100%) had positive outcomes after the fourth treatment vs. 66% (8/12) of the remaining eyes (p=0.25) in treatment 4.

Having thus examined whether those patients with the best outcomes after a given treatment fared better on subsequent treatment, we studied whether patients with poor funduscopic outcomes were predisposed towards failures of future treatment. In particular, we wished to determine whether there existed a specific number of failures after which the probability of future success became very unlikely. To address this goal, we examined whether consecutive failures of treatment were associated with significantly lower rates of success after the next treatment.

We found that eyes that had negative funduscopic outcomes after the first treatment had a similar rate of success on second treatment as eyes that had experienced positive outcomes (resolution *or* improvement of edema) after the first treatment. Of the 20 eyes that worsened after the first treatment, 50% had positive results after the second treatment. By comparison, of the 44 eyes that had positive results after the first

treatment, 56.8% (25 of 44) resolved or improved after the second treatment. The difference in success rates upon second treatment between these two groups was therefore not statistically significant (p=0.81). Thus a poor result after treatment 1 did not predict a poor result upon treatment 2.

We further observed that two consecutive funduscopic treatment failures resulted in a difference in success rates on the third treatment that approached statistical significance. Of the 7 eyes receiving a third treatment after failures of both of the first two treatments, 3 had positive funduscopic outcomes after treatment 3 (42.9%). In comparison, 26 of 33 of the remainder of eyes requiring a third treatment achieved a positive outcome on this treatment (79%) (p=0.075).

Finally, we found that eyes with 3 consecutive treatment failures were unlikely, by our analysis, to achieve positive outcomes on the fourth treatment. All 3 of the eyes that had negative outcomes in treatments 1 through 3 also had negative outcomes in the fourth treatment. By contrast, 14 of the remaining 15 eyes needing a fourth treatment (93.3%) had positive outcomes (p=0.0049). The difference in outcome on the fourth treatment between eyes that had experienced 3 consecutive failures vs. the remainder of eyes was therefore statistically significant.

Comparison of Visual Acuity Outcomes for each Treatment

After the first laser treatment, 21 of the 64 patients (32.8%) showed an improvement in best corrected visual acuity as documented by the Snellen chart, 22 (34.4%) were stable, and 21 (32.8%) had worsened visual acuity. Note that while the success rate (improvement or stabilization) amongst patients in the present analysis was roughly 67% compared to the 50% observed in the ETDRS trial, the follow-up interval we used for this calculation was 6 months, compared to 3 years in the ETDRS trial.

The proportion of eyes with stable or improved visual acuity vs. worsened visual acuity on subsequent treatment did not show a statistically significant difference from the first treatment. Following treatment 2, 14 eyes (21.9%) improved, 29 eyes (45.3%) were stable, and 21 eyes (32.8%) worsened. After treatment 3, 15 eyes (37.5%) improved, 14 eyes (35%) were stable, and 11 eyes (27.5%) worsened. Finally, after treatments ≥4, 4 eyes improved (22.2%), 9 eyes (50%) were stable, and 5 eyes (27.8%) worsened. Thus visual acuity was maintained in 67.2% of patients after treatment 2, 72.5% of patients after treatment 3, and 72.2% of patients after treatments ≥4. The p values for these success rates vs. that of treatment 1 were as follows: treatment 2 vs. treatment 1, p= 1.0; treatment 3 vs. treatment 1, p=0.73; treatment ≥4 vs. treatment 1, p=1.0. (*See figure 3 for a summary of the visual acuity outcomes after each laser treatment.*)

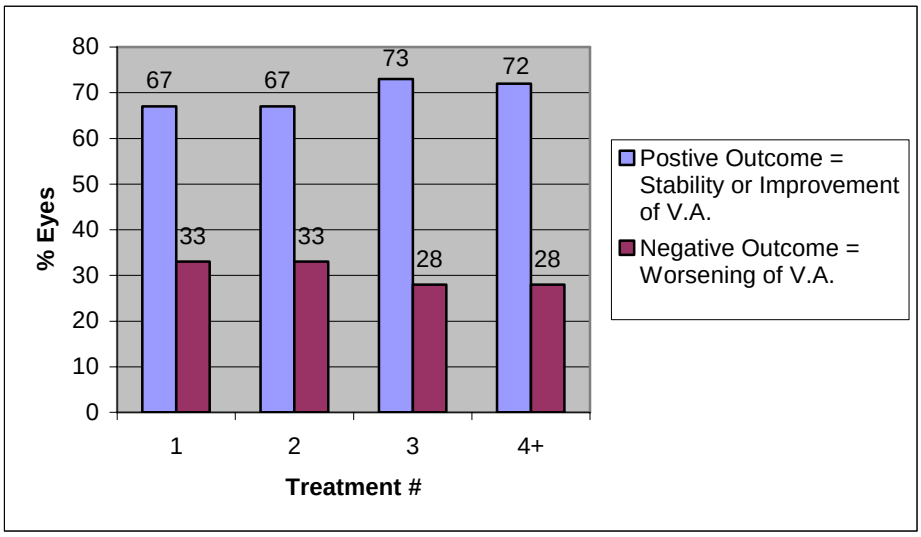

Figure 3: Percentage of Eyes with Positive and Negative Visual Acuity Outcomes for each Treatment. In this figure, positive outcomes are defined as stability or improvement of visual acuity at the 6 month follow-up after treatment. Negative outcomes are defined as worsening of visual acuity at 6 months after a given treatment. There is no significant difference between the success rate of the first treatment and that of subsequent treatments.

Visual Acuity Outcomes of Early Treatments as Predictors of Outcome after Repeated Laser Treatment:

As with funduscopic outcomes, we studied whether poor visual acuity outcomes after a given treatment predisposed patients for poor visual outcomes on subsequent treatments. Furthermore, we questioned whether there existed a specific number of treatment failures after which subsequent treatment was unlikely to be successful at maintaining visual acuity.

Worsening of visual acuity after the first treatment (failure of treatment by visual acuity criteria) was not associated with a lower rate of positive visual acuity outcomes in the next treatment. Of the 43 eyes that had improved or stable visual acuities (positive

outcome) after the first laser treatment, 29 (67.4%) showed positive visual acuity outcomes after treatment 2. In comparison, 66.7% of the 21 eyes with negative outcomes after the first laser treatment had positive outcomes after the second treatment (p=0.82). Thus visual acuity outcome after the first treatment did not predict success or failure upon retreatment.

Of the 40 eyes needing a third treatment, 7 had experienced negative visual acuity outcomes after both treatments 1 and 2. On the other hand, 33 had experienced a positive visual acuity outcome after at least 1 of the prior two treatments. Of the former group, all 7 achieved a positive outcome on the third treatment (100%). This is in comparison with a 66.7% (22/33) rate of positive outcomes in the third treatment amongst the remainder of eyes (p=0.16). Thus a poor visual acuity outcome after both treatments 1 and 2 was not associated with a statistically significant lower success rate upon treatment 3.

DISCUSSION

The use of multiple focal/ grid laser treatments for CSME poses an interesting clinical question, particularly with the recent introduction of intraocular steroid injection as a possible alternative treatment to laser photocoagulation.

We found that additional macular laser treatments for diabetic macular edema are effective in improving retinal thickness. This study supports the results of previous studies, whose conclusions suggest that repeat laser treatments for diabetic macular edema may be beneficial. For example, Yi et al. found that in a sample of 136 eyes that did not have resolution of CSME after the first laser treatment, resolution occurred upon subsequent treatment in 116 (85.6%) eyes (28).

According to our study, repeat laser treatments were also successful in maintaining visual acuity in the majority of patients with diabetic macular edema. This observation applied regardless of treatment number.

This study suggests that patients who had a recurrence of edema after full resolution with laser treatment may have a higher chance of a positive funduscopic outcome with retreatment than patients who had never achieved full resolution. For example, of patients undergoing a second treatment, close to 80% of those obtaining retreatment for recurrence of edema had positive funduscopic outcomes, versus roughly 50% of those who had incomplete responses to the first treatment ($p=0.048$). In the present analysis, we observed a trend suggesting that patients achieving full resolution of macular edema on any given treatment were more likely to have successful repeat treatments than their counterparts who had never achieved full resolution; however, a

statistically significant difference between these two groups was only observed on the first retreatment, i.e. treatment 2. It is important to note that the number of patients involved in treatments 3 and higher decreased, making a statistical difference between these two groups more difficult to detect. Furthermore, our results do not imply that re-treatment should not be attempted in those patients who failed to achieve complete resolution on early treatments, as a significant proportion of these patients have success on retreatment.

Our study further suggests that there may be a limit to how many times treatment should be reattempted if it has never produced positive results. The results imply that for patients with up to 2 negative outcomes on consecutive treatments, there is still a high likelihood of positive visual acuity outcomes from further treatment: in our study 100% of the 7 eyes receiving a third treatment after two consecutive failures to maintain visual acuity had successful visual acuity outcomes on the third attempt. Furthermore, just over 40% of the patients in our study who had funduscopic failures on their first 2 treatments had an improvement in their fundus exam after their third treatment.

However, if a patient fails three consecutive treatments, our study provides no evidence that further laser treatment would be beneficial. In terms of funduscopic findings, all three of the patients who had failed treatments 1-3 also failed subsequent treatment. This result is in comparison to a 93% success rate amongst the remainder of eyes ($p= 0.0049$) on the fourth treatment. .

Our study was started before the availability of optical coherence tomography at our center. Studies using ocular coherence tomography may prove beneficial because OCT would allow a quantitization of changes in macular edema. While this tool would

add important information to the analysis of the efficacy of repeated macular laser treatment, it is also worth noting that recent studies have shown that ocular coherence tomography corroborates findings on funduscopic exam (48). This observation suggests that the results of studies using OCT would support the current findings. Another limitation of the present study is that it is a retrospective case series; a prospective multicenter randomized clinical trial is needed to evaluate repeat macular laser treatments for persistent and recurrent macular edema.

The results of this study suggest that repeated laser photocoagulation treatments for CSME are effective and that the majority of eyes receiving repeat treatments will respond with improvement in macular edema and stability or improvement of visual acuity. However, given the existence of viable alternatives, it is important for treatments >3, to consider whether the patient has ever responded positively to prior treatments. The results of our study do not provide support for continuing focal/grid laser treatments for patients who have had three consecutive treatment failures.

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