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Effect of Focal/Grid Photocoagulation on Visual Acuity and Retinal Thickening in Eyes with Non-Center Involved Clinically Significant Diabetic Macular Edema

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Abstract

Purpose—To report visual acuity and anatomic changes from baseline to 12 months after modified ETDRS style (focal/grid) photocoagulation in eyes with non-center involved (non-CI) clinically significant macular edema (CSME).

Methods—Visual acuity, optical coherence tomography, fluorescein angiography, and fundus photography data were analyzed from eyes with non-CI CSME treated with modified ETDRS style (focal/grid) photocoagulation in a Diabetic Retinopathy Clinical Research Network trial.

Results—Among the 22 eyes (of 22 patients) with 12 month follow-up, median visual acuity letter score remained within one letter of baseline over 12 months. The median central subfield retinal thickness decreased by 10 μ m, median total macular volume decreased by 0.2mm³, and median fluorescein leakage area within the grid decreased by 0.7 disc areas.

Conclusions—We are unaware of any other systematic evaluation of eyes with non-CI CSME since the ETDRS. Focal/grid laser in these non-CI eyes was associated with relatively stable visual acuity and retinal thickness measurements, and decreased fluorescein leakage area at 1 year. One year visual acuity results are consistent with those published by the ETDRS, despite the intervening significant differences in the management of diabetes. Although this was a small study without a concurrent control group, the ETDRS recommendation to consider focal/grid laser in eyes with non-CI CSME still seems appropriate.

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Keywords

Diabetic macular edema; focal/grid laser photocoagulation

Introduction

Macular edema is a major cause of central vision impairment in persons with diabetic retinopathy. To date, demonstrated means to reduce the risk of vision loss from diabetic macular edema (DME) include focal laser photocoagulation,^{1, 2} intensive glycemic control,³ and blood pressure control.⁴ In the Early Treatment Diabetic Retinopathy Study (ETDRS), focal photocoagulation of eyes with clinically significant macular edema (CSME) reduced the risk of moderate visual acuity loss (defined as a loss of 15 or more letters) by approximately 50% (from 24% to 12%) three years after initiation of treatment.¹ In eyes with less severe retinal thickening at the center of the macula on baseline stereoscopic color photographs, the ETDRS reported “trends” (not achieving statistical significance) for lesser magnitude of the laser treatment effect on 1) rates of reduction in moderate visual loss (defined as a doubling or more of the visual angle) and 2) rates of visual acuity less than 20/100 at each follow up visit (1, 2, 3, 4 and 5 years).⁵ As new drugs have been developed to target earlier stages of diabetic retinopathy and DME,⁶ it is anticipated that future clinical trials will evaluate efficacy for earlier stages of disease, which might include eyes with non-center involved (non-CI) CSME. Therefore, further investigation regarding a potential differential effect of the gold standard treatment, photocoagulation, in eyes with non-CI CSME is warranted. To our knowledge, a recent study conducted under the auspices of the Diabetic Retinopathy Clinical Research Network (DRCR.net) is the only published clinical trial since the ETDRS to evaluate the efficacy of modified ETDRS style (focal/grid) laser photocoagulation in eyes with non-CI CSME.⁷ Given the differences in metabolic control between the pre-1985 ETDRS trial and those currently achieved (e.g. over 40% of patients in the ETDRS had a hemoglobin A1c level $\geq 10\%$ ⁸ compared with 17% in the recent DRCR.net study⁷), visual acuity response to laser in eyes with non-CI CSME may differ now as compared to that observed in the ETDRS. In the current era, anatomic response to laser treatment can be assessed from optical coherence tomography (OCT), an imaging modality which was unavailable at the time of the ETDRS.

The purpose of the current study is to report the visual acuity and anatomic changes from baseline to 12 months after modified ETDRS (focal/grid) photocoagulation in eyes with non-CI CSME in a recently conducted multicenter randomized controlled clinical trial⁷ comparing two methods of laser photocoagulation for DME.

Methods

Data were analyzed from the DRCR.net randomized trial which compared modified ETDRS style (focal/grid) laser photocoagulation to mild macular grid laser photocoagulation for DME (mETDRS vs MMG trial).⁷ The design, methods, and results of the photocoagulation trial have been published,⁷ and complete details are available at <http://drcr.net>. One or both eyes of participants had to meet the following major ocular criteria to be enrolled in the randomized trial: (1) best-corrected ETDRS visual acuity letter score ≥ 19 (approximately 20/400 or better), (2) definite retinal thickening due to previously untreated DME within 500 microns of the macular center on clinical examination, and (3) mean retinal thickness of ≥ 250 microns in the central subfield and/or ≥ 300 microns in at least one of the four inner subfields on the fast macular map scan obtained using a Stratus OCT. Best corrected electronic—ETDRS visual acuity measurements and OCT scans were performed on all participants at baseline and 3.5, 8, and 12 months after study entry. Fundus photographs and fluorescein angiography were obtained at baseline and 12 months, and were graded by the Fundus Photograph Reading Center

of the University of Wisconsin, Madison. All study eyes had photocoagulation performed at baseline. Photocoagulation was repeated during follow up according to specified study guidelines if DME did not meet deferral criteria. In general, retreatment was to be administered unless the DME had resolved or there was substantial improvement in the DME in the opinion of the investigator (e.g., >50% decrease in the total macular-thickened area or >50% decrease in retinal thickening shown by OCT in central or inner subfields with previous retinal thickening). The trial adhered to the tenets of the Declaration of Helsinki. For the current report, month 12 was selected as the endpoint because in the mETDRS vs MMG trial 1) baseline electronic—ETDRS visual acuity measurements, OCT, fundus photographs, and fluorescein angiograms were all obtained at baseline and 12 months, and 2) the protocol specified that after month 12, therapies other than laser photocoagulation could be employed to treat DME at the investigator's discretion. OCT scans were sent to the Reading Center where they were visually inspected. For 19% of the 323 baseline scans and 13% of the 872 follow-up scans, the automated thickness measurements were judged to be inaccurate and center point thickness was manually determined and used to impute a value for the central subfield using a regression equation (since the correlation of the two measures is 0.99).⁷ A total of 263 subjects from 79 sites were enrolled in the mETDRS vs MMG trial. In 60 of these participants both eyes were eligible and, thus, there were 323 study eyes. Study eyes were randomized to receive laser photocoagulation following one of two protocols for treatment of DME at baseline. There were no untreated study eyes. Of the 323 eyes that were candidates for analysis in this report, 42 had non-CI CSME (defined as a baseline central subfield thickness [CST] <250 microns and a baseline photograph assessment of retinal thickness at the center of the macula graded as “none” or “questionable”). Because the DRCR.net mETDRS vs MMG trial demonstrated that, at 12 months after initial treatment assignment, the MMG technique was less effective at reducing OCT-measured retinal thickening than the mETDRS approach,⁷ Network investigators recommended that the mETDRS style laser technique remain the gold standard laser approach to manage eyes with CSME. Accordingly, we have elected to report on only those eyes that were randomly assigned to mETDRS style treatment. Thus, 18 eyes in the non-CI CSME group were excluded from this analysis as they were assigned to the MMG technique, and this report evaluates the 24 eyes with non CI CSME treated with mETDRS. The modifications of the ETDRS method of photocoagulation used in this study were for exclusive use of a 50 micron spot size (versus up to 200 microns for grid treatment in the ETDRS), use of yellow or green wavelengths (versus use of argon blue-green in the ETDRS), and in general a lesser intensity of laser burns (barely visible [light gray]) for the endpoint (versus “above threshold but less intense than panretinal photocoagulation burns” in the ETDRS).^{7, 9}

Results

Twenty-two of 24 patients in this analysis completed their 12-month follow-up examination. The mean number of focal/grid laser treatments administered was 1.4. Baseline visual acuity, OCT, fluorescein angiography (FA) and stereoscopic color fundus photograph characteristics of the study eyes are shown in Table 1.

Changes in these variables from baseline to 12 months after focal/grid photocoagulation are summarized in Table 2. Median visual acuity letter score decreased by one letter. Eighteen percent (4/22) of eyes had a visual acuity improvement of ≥ 5 letters and 32% (7/22) had a decrease of ≥ 5 letters. Median retinal thickness was reduced 4 to 12 microns (depending on the OCT parameter assessed) and median retinal volume was reduced 0.2mm³ and 0.1mm³ for total macular volume and inner zone volume, respectively. Eighteen percent (4/22) of eyes had a decrease in central subfield thickness of ≥ 25 microns. The area of fluorescein leakage within the grid decreased by 0.7 disc areas, and DME area within the grid on fundus photography increased by 0.21 disc areas. Forty-four percent (8/18) of eyes had a decrease in fluorescein leakage area of ≥ 1 disc area. Most (15, or 68%) eyes remained within 1 level of their baseline

ETDRS DME severity level,⁸ 7 (32%) eyes worsened by 2 or more levels, and none improved by 2 or more levels.

Discussion

To our knowledge, this is the only study since the ETDRS primary report in 1985 to evaluate the efficacy of focal/grid laser photocoagulation in eyes with non-CI CSME. In the current study, visual acuity remained stable at 12 months after focal/grid photocoagulation. However, 23 of the 24 eyes included in this analysis had a visual acuity letter score of 68 or better (approximately 20/40-1 or better), with the remaining eye having a visual acuity letter score of 50 (approximately 20/100); therefore, the opportunity to have moderate vision improvement was limited in most study eyes and the study results should not be generalized to patients with poorer levels of baseline visual acuity.

Median OCT-measured thickness and volume measurements were relatively stable at 12 months. The four eyes (18%) that had a decrease in central subfield thickness of ≥ 25 microns likely had some center-involved edema at baseline. The reduction in median disc areas of fluorescein leakage, as well as the fact that 44% of eyes demonstrated a decrease in fluorescein leakage area of ≥ 1 disc area, supports a beneficial effect of laser treatment in eyes with non-CI CSME, and suggests that evaluation of fluorescein leakage area may be useful when evaluating response to early stage non-CI CSME therapies.

Median area of DME within the grid, as assessed by graders of fundus photographs at a reading center, increased despite relatively stable OCT indices and reduced fluorescein leakage area. This may be due, at least in part, to the fact that the grid used to assess fundus photographs is 44% larger than the grid used to assess OCT variables¹⁰ and, therefore, areas of increased thickening present on fundus photographs may not be located within the area sampled by OCT imaging. In addition, given the small magnitude of changes in retinal thickening measured and the inherent variability in the subjective evaluation of color photographs by graders, this apparent discrepancy may not be significant.

A worsening in ETDRS DME severity level of 2 or more levels was observed in 32% of eyes, and an improvement in ETDRS DME severity level of 2 or more levels was observed in 0%. This is not surprising given the ceiling effect (67% of eyes with non-CI CSME had an ETDRS DME severity level of 1 at baseline and, therefore, could not improve by 2 or more levels).

In conclusion, focal/grid laser in eyes with non-CI CSME was associated with relatively stable visual acuity and OCT thickness and volume measurements, and decreased fluorescein leakage area at 1 year after treatment. Our one year visual acuity results are consistent with those published by the ETDRS, despite the intervening significant differences in the management of diabetes. Most patients retain good visual acuity a year after treatment (75% were 20/25 or better). Although this a small study and there is no concurrent control group, the ETDRS recommendation to consider focal/grid laser in eyes with non-center involved CSME still seems appropriate.

Summary Statement: To our knowledge, this is the first report since the ETDRS to evaluate focal/grid laser for non-center-involved CSME. Laser was associated with stable acuity and retinal thickness, and decreased fluorescein leakage area at 1 year. Acuity results are consistent with those of the ETDRS, despite intervening differences in diabetes management.

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Table 1

Baseline Visual Acuity, Optical Coherence Tomography (OCT), Fluorescein Angiography (FA) and Stereoscopic Color Fundus Photograph Characteristics - median (25th, 75th percentiles) or N (%)

	Eyes with Non-Center Involved CSME N = 24
Visual acuity letter score	84 (76, 90)
Snellen equivalent	20/20 (20/32, 20/16)
$\geq 20/16$	10 (42%)
20/20	2 (8%)
20/25	4 (17%)
20/32	4 (17%)
20/40	2 (8%)
$\leq 20/50$	2 (8%)
OCT characteristics	
Central subfield (microns)	225 (213, 236)
Total macular volume^a (mm ³)	8.0 (7.5, 8.2)
Mean inner zone unweighted thickness^b (microns)	282 (274, 289)
Inner zone volume^c (mm ³)	2.0 (2.0, 2.1)
Mean unweighted thickness within the grid^d (microns)	281 (266, 290)
Max inner subfield thickness (microns)	312 (305, 324)
Fluorescein angiography characteristics - disc areas	
Fluorescein leakage within the grid^e	1.99 (1.22, 8.40)
Cystoid abnormality within the grid^f	0 (0, 0)
Capillary loss within the grid^g	0 (0, 0.04)
Fundus photograph characteristics	
DME area within the grid - disc areas	1.85 (0.49, 3.24)
ETDRS severity scale - N (%)	
Level 1	16 (67%)
Level 2	5 (21%)
Level 3	3 (13%)

^aMissing for 5 eyes

^bMissing for 1 eye

^cMissing for 3 eyes

^dMissing for 1 eye

^eMissing for 1 eye

^fMissing for 1 eye

^gMissing for 7 eyes

Table 2

Change in Visual Acuity, Optical Coherence Tomography (OCT), Fluorescein Angiography (FA) and Stereoscopic Color Fundus Photograph Characteristics from Baseline to 12 Months After Focal/Grid Photocoagulation - median (25th, 75th percentiles) or N (%)

	Eyes with Non-Center Involved CSME N = 22 ^a
Visual acuity letter score	-1 (-5, +2)
≥ 15 letters improvement	0
10-14 letters improvement	1 (5%)
5 - 9 letters improvement	3 (14%)
within ± 4 letters	11 (50%)
5 - 9 letters worse	4 (18%)
10-14 letters worse	1 (5%)
≥ 15 letters worse	2 (9%)
OCT characteristics	
Central subfield (microns)	-10 (-16, +13)
Total macular volume ^b (mm ³)	-0.2 (-0.5, +0.1)
Mean inner zone/center unweighted thickness ^c (microns)	-8 (-20, +13)
Inner zone volume ^d (mm ³)	-0.1 (-0.1, +0.1)
Mean unweighted thickness within the grid ^e (microns)	-4 (-18, +8)
Max inner subfield thickness ^f (microns)	-12 (-27, +11)
<i>Excluding the Central Subfield:</i>	
Mean inner zone subfields thickness ^g (microns)	-9 (-23, +15)
Mean outer zone subfields thickness ^h (microns)	-4 (-15, +19)
Fluorescein angiography characteristics - Disc Areas	
Fluorescein leakage within the grid ⁱ	-0.70 (-2.06, +0.16)
Cystoid abnormality within the grid ^j	0 (0, 0)
Capillary loss within the grid ^k	0 (0, +0.01)
Fundus photograph characteristics	
DME area within the grid - disc areas	+0.21 (-0.47, +5.05)
ETDRS severity scale	
≥ 2 levels better	0
Within 1 level	15 (68%)
≥ 2 levels worse	7 (32%)

^aExcludes 2 subjects who did not complete 12 month visit

^bMissing for 6 eyes

^cMean thickness of central subfield and 4 inner subfields, Equal weight to all 5 zones. Missing for 2 eyes

^dMissing for 5 eyes

^eMean thickness of central subfield, 4 inner subfields, and 4 outer subfields. Equal weight to all 9 zones. Missing for 2 eyes

^fMaximum of central subfields and 4 inner subfields

^gMean thickness of 4 inner subfields (excluding the center), Missing for 2 eyes

^hMean thickness of 4 outer subfields (excluding the inner and center), Missing for 2 eyes

ⁱMissing for 4 eyes

^jMissing for 4 eyes

^kMissing for 8 eyes