Evaluation of Grid Pattern Photocoagulation for Macular Edema in Central Vein Occlusion

The Central Vein Occlusion Study Group M Report

*The Central Vein Occlusion Study Group**

Purpose: To evaluate the efficacy of macular grid photocoagulation in preserving or improving central visual acuity in eyes with macular edema due to central vein occlusion (CVO) and best-corrected visual acuity of 20/50 or poorer.

Methods: Patients with angiographically documented macular edema due to CVO were entered into a multicenter randomized controlled clinical trial supported by the National Eye Institute. Eligibility was determined based on both clinical examination findings and photographic documentation evaluated at a photograph reading center. Eyes were assigned randomly to macular grid photocoagulation (77 eyes) or no treatment (78 eyes). Patients were followed every 4 months for 3 years or until the end of the study. The outcome measure was visual acuity.

Results: The study population consisted of 155 eyes in 155 patients. There was no difference between treated and untreated eyes in visual acuity at any point during the follow-up period. Initial median visual acuity was 20/160 in treated eyes and 20/125 in control eyes. Final median visual acuity was 20/200 in treated eyes and 20/160 in control eyes. However, treatment clearly reduced angiographic evidence of macular edema.

Conclusion: The results of this study do not support a recommendation for macular grid photocoagulation for the population meeting the Central Vein Occlusion Study macular edema group eligibility criteria. *Ophthalmology 1995;102:1425–1433*

Previous studies have shown that decreased vision from macular edema is common in eyes with central vein occlusion (CVO).[1,2] Randomized clinical trials in other retinal vascular diseases have shown improved visual prognosis with argon laser photocoagulation for macular edema. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that focal photocoagulation of "clinically significant" diabetic macular edema substantially reduces the risk of visual loss.[3] The Branch Vein Occlusion Study demonstrated a small but definite benefit of macular grid photocoagulation for persistent macular edema.[4] In CVO, although an uncontrolled pilot study of laser treatment for macular edema due to CVO suggested some benefit,[5] photocoagulation for macular edema due to CVO

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* Members of the Central Vein Occlusion Study Group are listed in the Appendix at the end of this article.

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has not been evaluated in a collaborative, prospective, controlled clinical trial.

Macular edema after CVO is typically due to diffuse capillary leakage and not due to focal microaneurysmal dilation similar to that seen in early diabetic retinopathy. For this reason, a grid pattern of photocoagulation was selected as the treatment modality similar to the Branch Vein Occlusion Study as opposed to the focal treatment used predominantly in the ETDRS.

Macular edema is self-limited in some retinal vascular diseases, and in the Branch Vein Occlusion Study the untreated control group of patients with macular edema actually showed some improvement in visual acuity. For these reasons, the eligibility criteria from group M in the Central Vein Occlusion Study (CVOS) group required a best-corrected visual acuity of 20/50 or worse, and also included a period of observation of at least 3 months from the onset of the CVO.

We present here the results of a multicenter, randomized, controlled clinical trial designed to compare the visual outcome of grid pattern photocoagulation and observation in eyes with CVO and reduced visual acuity (20/50 or worse) associated with macular edema. This trial was one of several studies conducted by the CVOS group. The study design and baseline findings for the CVOS were published previously, along with selected natural history findings.[6–8]

Materials and Methods

Recruitment began August 1, 1988, and was carried out in the nine clinics listed in the Appendix section. The last patient was entered on August 12, 1992. Patients were followed for 3 years or until the end of the study on February 28, 1994.

Eligibility and Exclusion Criteria

Eligibility and exclusion criteria for group M are summarized in Table 1. Patients had to have visual acuity of 20/50 or worse at entry. To ensure that patients whose vision already was improving were not included, two visits were performed before entry, with an interval between them of at least 2 weeks. Patients whose vision had improved by two lines (10 letters) or more on the CVOS visual acuity chart were declared at least temporarily ineligible. For the purpose of this study, CVO was defined as photographically documented retinal hemorrhage in all four quadrants with a dilated venous system. If nonperfusion was present in the macula, the patient was excluded. Patients with evidence of any intercurrent retinal vascular disease in the study eye or any diabetic retinopathy (by clinical examination, stereo color photography or fluorescein angiography) or definite age-related macular degeneration in either eye were excluded. Aphakia, pseudophakia, or clinically significant lens opacity of the study eye were additional exclusion criteria.

Table 1. Eligibility and Exclusion Criteria

Eligibility Criteria
Confirmed presence of CVO
CVO of at least 3 mos' duration
Macular edema involving fovea confirmed by the Reading Center based on fundus fluorescein angiography
Visual acuity between 5/200 and 20/50 with no explanation apparent for decreased acuity except for CVO
Phakic with clear media
No improvement in visual acuity on consecutive visits prior to entry
Intraocular pressure < 30 mmHg
Ability to obtain good quality fundus photographs and fluorescein angiography
Willingness to sign consent form
Exclusion Criteria
Previous photocoagulation for retinal vascular disease of the study eye
Intercurrent eye disease that is likely to affect visual acuity over study period
Presence of any diabetic retinopathy in either eye, new or old branch arterial/vein occlusion in study eye, retinal neovascularization in study eye, other retinal vascular disease in study eye, or vitreous hemorrhage other than breakthrough in study eye
Presence of peripheral anterior synechia in the study eye
Heparin/warfarin sodium cannot be discontinued for duration of study

CVO = central vein occlusion.

Patient Entry

Random treatment assignments were made using computer-generated random allocation. Separate random treatment assignment lists were generated at the beginning of the study for each clinic and for patients with duration of CVO of less than 1 year and for those with duration greater than or equal to 1 year. After an orientation session regarding the CVOS, a detailed initial visit was performed for each patient, including medical and ophthalmologic history, blood pressure measurement, protocol visual acuity examination, intraocular pressure measurement, and slit-lamp examination, including gonioscopy and color slit-lamp iris photography with pupils undilated. A dilated slit-lamp and fundus examination was followed by color stereo fundus photography of both eyes and fundus fluorescein angiography with a transit of the affected eye. The investigator discussed the study protocol with each patient, who read and signed a consent form. Photographs were sent to the Photograph Reading Center and forms were sent to the Coordinating Center for determination of eligibility.

If protocol pictures and forms were judged satisfactory by the Photograph Reading Center and Coordinating Center, patients returned to the clinic within 4 weeks of the date of the eligibility angiogram for an abbreviated confirmatory

examination. Random assignment then was obtained from the Coordinating Center by telephone. If the patient was assigned to treatment, the treatment was generally performed that day. Patients returned for follow-up visits every 4 months for 3 years or until the end of the study.

Photography Protocol

Color fundus photographs were taken at baseline and at each follow-up visit for all patients. For treated patients, color fundus photographs also were taken within 48 hours after treatment. Fluorescein angiograms of the fundus were taken at baseline, at the 4-month visit, and at each annual visit.

Zeiss stereo color photographs of the macula were required in addition to the standard CVOS fundus photographs using the wide-angle fundus camera (Canon 60° [Canon USA, Inc, Lake Success, NY] or Topcon 45° [Topcon America Corp, Paramus, NJ]). Eyes that did not dilate adequately for wide-angle fundus photography were photographed using the 30° Zeiss fundus camera (Karl Zeiss, Oberkochern, Germany). A timed fundus fluorescein angiogram was obtained with the same type of camera as used for the color fundus photographs. After 30 seconds, a sweep, which included all of the protocol fields in the midperiphery, was obtained.

Grid Laser Treatment and Retreatment

For eyes assigned to treatment, grid laser photocoagulation was carried out using the Coherent Radiation green argon laser with slit-lamp delivery system. The initial treatment was applied according to the guidelines given in Table 2. The fluorescein angiogram taken at the initial visit was used as a treatment guide. Treatment was applied within 4 weeks of the time the initial angiogram was made.

At the 4-month visit after treatment and at each annual visit, the Photograph Reading Center evaluated the results of treatment by comparing the pretreatment fluorescein angiogram with the follow-up fluorescein angiogram and by assessing the change in visual acuity. If improvement in visual acuity was nine letters or less and treatable macular edema was present angiographically, the patient was scheduled for retreatment. Follow-up treatment was performed using a fluorescein angiogram made within the previous 28 days. Retreatment parameters were identical to initial treatment parameters except that previously treated areas were avoided and treatment was applied to areas of previously untreated leaking capillaries as well as to areas of persistent leakage.

Visual Acuity Measurements

The primary outcome for group M eyes was visual acuity. The protocol refraction and visual acuity measurements were adapted from procedures and equipment developed for the ETDRS. Trained and certified visual acuity examiners performed a complete refraction and measured visual acuity of the study eye every 4 months at all annual and nonannual visits. The ETDRS chart and box for retroillumination were obtained for each clinic from Lighthouse Low Vision Services of New York. This chart was designed with five high-contrast Sloan letters in each of 14 lines, lines of equal difficulty, and a geometric progression of letter size from line to line, so that a difference of any three lines (15 letters) represents doubling of the visual angle. Visual acuity was tested at 4 m. When four or more letters were read correctly, the visual acuity score was the number read correctly plus 30. If fewer than four letters were read correctly at 4 m, visual acuity was tested at 1 m. In this case, the visual acuity score was the number read at the 1-m distance. If no letters were read correctly at 1 m, the visual acuity score was zero, and the patient's visual acuity was classified as E card at 0.5 m, light perception only, or no light perception.

In every clinic except one, each visual acuity examiner was masked as to the patient's treatment assignment. In one clinic, masking was operationally difficult and not enforced. If results for this clinic are deleted from the analysis, the conclusions are not changed.

Table 2. Initial Treatment Parameters

Treatment covered only the area of leaking capillaries in a grid pattern spaced approximately one half to one burn width apart
Treatment covered all of the areas of leaking capillaries within 2 disc diameters of the center of the fovea; could not extend beyond 2 disc diameters from the fovea and could not extend within the foveal avascular zone
Treatment avoided collateral vessels
Treatment was avoided over retinal hemorrhage
Initial macular treatment was not to be staged but completed in one session
Treatment parameters were as follows
Spot size, 100 μm
Intensity, moderately intense whitening of the retina
Duration, 0.1 secs
Anesthesia, topical or retrobulbar

Grading of Macular Edema

Macular edema was judged using the fluorescein angiogram. To be eligible, macular edema had to involve the center of the fovea. If nonperfusion was present in the macula, the patient was excluded. The geographic area of macular edema in disc areas was measured at the Photograph Reading Center at baseline and at each follow-up visit where a fluorescein angiogram was obtained. In addition, the change in intensity of fluorescein staining from the previous fluorescein angiogram was recorded.

Statistical Methodology

Visual acuity score and change in visual acuity are reported using frequency distributions and are summarized using means. Differences in means between treated and untreated eyes were assessed using Student's t test and 95% confidence intervals. For purposes of this report, a

subject with "E card" vision at a visit was assigned a visual acuity score of −12, which is three lines worse than the 20/800 line on the chart at 1 m. A subject with visual acuity of "light perception only" was assigned a score of −27, six lines worse than the 20/800 line. The effect of treatment on disc areas of macular edema was assessed using the Wilcoxon rank-sum test. $P < 0.05$ is considered significant.

Several baseline factors were examined to determine whether a treatment interaction existed with each factor (i.e., whether the impact of treatment on change in visual acuity depended on the value of each factor). The interaction of treatment with continuous factors was assessed using analysis of covariance. These factors included baseline visual acuity, age, blood pressure, intraocular pressure, and baseline disc areas of macular edema. The interaction of treatment with qualitative factors was assessed by coding each factor as a binary variable (presence or absence of the factor) and testing the significance of the treatment-factor interaction term in a 2 × 2 analysis of variance model. These factors included male gender, history of smoking, duration of CVO greater than 1 year, extensive retinal hemorrhage, moderate or severe venous tortuosity, cotton-wool spots, macular exudates, intraretinal microvascular changes, blunting and staining of venules, and venous collaterals on the disc. Bonferroni's inequality was used to adjust the probability values for these 15 post-hoc subgroup analyses.

Results

The Patient Population

Of the 155 patients entered into the macula study, 77 were randomized to grid laser treatment and 78 to observation without treatment (control). The baseline characteristics were reported previously[6,7] and are summarized in Table 3. In general, the patients were older than 60 years of age and almost 60% were male. Visual acuity ranged from 20/50 to 5/200. The treated and untreated groups were well matched with respect to visual acuity and all other major baseline characteristics.

Description of Treatment

The median number of treatment spots applied during all treatment sessions was 143 (range, 37–798 spots). The spot size used in all patients was 100 μm. Twenty-three of the 77 patients assigned to treatment received follow-up treatment of the macula from 79 to 1000 days after the initial treatment. This follow-up treatment occurred shortly after the 4-month visit in most of the patients (14/23). Four patients had an additional follow-up treatment session. Each treatment report included queries regarding complications; there were no cases of treatment in the foveal avascular zone, no rupture of Bruch membrane, no choroidal hemorrhage, and no vitreous hemorrhage resulting from initial or follow-up treatment.

Table 3. Selected Baseline Characteristics for Treated and Untreated Eyes

Characteristics	Treated	Untreated	P
No. of eyes	77	78	
Specified characteristics (%)			
Age (yrs)			
<60	29	22	0.47
60–74	45	55	
≥75	26	23	
Male	66	53	0.10
White	92	96	0.38
Smoker			
Present	12	13	1.00
Past	48	46	
Duration of CVO			
<1 mo	0	1	0.57
<1 yr	52	56	
≥1 yr	48	42	
Visual acuity			
20/20 or better	0	0	0.60
20/25–20/40	0	0	
20/50–20/100	39	46	
20/125–20/200	36	35	
20/250–5/200	25	19	
<5/200	0	0	
Disc areas of macular edema			
None	0	0	0.63
<2	3	3	
2 to < 5	36	44	
≥5	61	53	
Unavailable	0	1	
Disc areas of nonperfusion			
None	29	42	0.44
<5	35	32	
5 to < 10	13	10	
≥10	13	8	
Unavailable	10	8	

CVO = central vein occlusion.

Quality and Completeness of Follow-up

Three major violations to the protocol occurred during the study. One patient was assigned to no treatment, but received initial and follow-up macula treatment in a clinic outside of the study. In this report, the results for the patient are retained in the control group as originally assigned. One patient in the treatment group was later determined to have been ineligible at the time of entry because of atrophy in the retinal pigment epithelium in the macula. One patient was randomized only 7 days after the initial study visit. The protocol required at least a 14-day interval between the initial visit and randomization. All three of these patients are included in the results.

The available follow-up information is shown in Table 4. Of the 155 patients entered, 88 completed 3 years of follow-up, 47 enrolled after February 1991 were followed until the end of the study, and 20 had incomplete follow-

Table 4. Available Follow-up Information by Treatment Allocation*

	Treated	Untreated
Initial visit	77	78
1 yr	73	75
2 yrs	60	56
3 yrs	46	42

* Values are number of patients followed for at least the specified duration.

up. Nine of these 20 patients died during the course of the study; 2 of these 9 had no follow-up visits. An additional 5 of the 20 patients were seen outside the study clinics either at home or in a nonstudy clinic; 2 of these 5 patients had no prior missed visits. The remaining 6 of the 20 patients were lost to follow-up, missing at least the last two expected visits.

Visual Acuity Results

There were no significant differences between treated and untreated patients at any follow-up visit in either level of visual acuity or in change in visual acuity. Table 5 shows the level of visual acuity for treated and untreated patients at baseline, at 4 months, and at each annual follow-up visit. At 36 months, eyes in the treated group had a mean visual acuity score of 39 letters, compared with 43 letters for the untreated group, for a mean difference of −4 letters (95% confidence interval for treated minus untreated, −15.2 to 5.9 letters). Table 6 shows the change in visual acuity from baseline for treated and untreated patients at 4 months and at each annual follow-up visit. The mean changes in visual acuity score from baseline to the 36-month visit was a loss of four letters in treated eyes and a three-letter loss in untreated eyes (95% confidence interval for the difference, −10.6 to 8.0, with negative values favoring no treatment). Figure 1 shows the mean change in visual acuity from baseline at each regularly scheduled follow-up visit by random treatment assignment. Thirty-three percent (25/75) of treated eyes and 29% (22/77) of untreated eyes lost at least two lines of vision (10 letters) between baseline and the final follow-up visit. Twenty-three percent (17/75) of treated eyes and 18% (14/77) of untreated eyes improved by two or more lines. Final median visual acuity was 20/200 in treated eyes and 20/160 in control eyes.

Subjects with duration of CVO less than 1 year and with duration of 1 year or more are shown in Figures 2 and 3, respectively. These graphs show the mean change in visual acuity by random assignment for these two groups. There were no differences found between treated and untreated eyes within either duration group.

The visual acuity results were consistent over all clinics and subgroups, except that there was an interaction between the treatment effect and age. Figures 4 and 5 show the change in visual acuity from baseline to the final CVOS visit by age at entry for treated eyes and untreated eyes, respectively. For treated patients, visual acuity tended to deteriorate in patients older than 60 years of age and to improve in younger patients. The untreated patients showed less evidence of the effect of age. This interaction between treatment effect and age was not statistically significant when adjusted for the number of potential interactions examined (nominal $P = 0.03$; with Bonferroni adjustment for 15 subgroup comparisons $P = 0.49$).

Further analysis of the 17 patients whose vision improved after treatment was performed to identify a subgroup that might respond well to treatment. Most of these eyes (11/17) came from a small subgroup (n = 24) treated and untreated patients who were younger than 60

Table 5. Number (%) of Eyes with Specified Visual Acuity at Baseline, 4 Months, and Each Annual Follow-up Visit by Treatment Allocation

	Baseline		4 Mos		12 Mos		24 Mos		36 Mos	
	Treated	*Untreated*	*Treated*	*Untreated*	*Treated*	*Untreated*	*Treated*	*Untreated*	*Treated*	*Untreated*
Visual acuity (no. of letters)										
20/20-better (83+)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (5)	0 (0)	2 (4)	0 (0)
20/25-20/40 (68-82)	0 (0)	0 (0)	2 (3)	3 (4)	7 (10)	3 (4)	5 (9)	3 (6)	4 (9)	5 (12)
20/50-20/100 (48-67)	30 (39)	36 (46)	23 (31)	24 (32)	14 (21)	20 (28)	13 (23)	19 (36)	12 (26)	12 (29)
20/125-20/200 (33-47)	28 (36)	27 (35)	26 (35)	33 (43)	21 (31)	33 (46)	14 (25)	16 (30)	9 (20)	14 (33)
20/250-5/200 (3-32)	19 (25)	15 (19)	23 (31)	16 (21)	25 (37)	15 (21)	18 (32)	14 (26)	16 (35)	9 (21)
<5/200 (1-2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	0 (0)	1 (2)	0 (0)
E card at 0.5 m	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	1 (2)	0 (0)	1 (2)
Light perception only	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)	2 (4)	1 (2)
No light perception	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total no. of eyes	77	78	74	76	68	72	57	53	46	42
Mean score (letters)	42	44	39	43	37	41	37	43	39	43
P	0.28		0.08		0.14		0.17		0.39	
95% confidence interval for difference in mean scores (treated minus untreated)	−6.6 to 1.9		−9.8 to 0.5		−10.8 to 1.5		−14.3 to 2.5		−15.2 to 5.9	

Table 6. Number (%) of Eyes with Specified Change in Visual Acuity from Baseline at 4 Months and at Each Annual Follow-up Visit by Treatment Allocation

	4 Mos		12 Mos		24 Mos		36 Mos	
	Treated	*Untreated*	*Treated*	*Untreated*	*Treated*	*Untreated*	*Treated*	*Untreated*
Visual acuity change in letters								
+40 or more (better)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)
+20 to 39	3 (4)	0 (0)	0 (0)	2 (3)	3 (5)	1 (2)	3 (7)	2 (5)
+15 to 19	1 (1)	1 (1)	4 (6)	2 (3)	7 (12)	4 (8)	7 (15)	3 (7)
+10 to 14	1 (1)	1 (1)	6 (9)	2 (3)	2 (4)	4 (8)	3 (7)	4 (10)
+5 to 9	11 (15)	13 (17)	10 (15)	11 (15)	9 (16)	8 (15)	4 (9)	5 (12)
−4 to +4	30 (41)	45 (59)	12 (18)	23 (32)	14 (25)	10 (19)	12 (26)	8 (19)
−5 to 9	10 (13)	6 (8)	11 (16)	10 (14)	1 (2)	13 (25)	2 (4)	7 (17)
−10 to 14	7 (9)	5 (7)	10 (15)	13 (18)	3 (5)	4 (8)	3 (7)	6 (14)
−15 to 19	4 (5)	4 (5)	7 (10)	6 (8)	6 (11)	5 (9)	3 (7)	2 (5)
−20 to 39	5 (7)	1 (1)	5 (7)	2 (3)	10 (18)	2 (4)	6 (13)	2 (5)
−40 or more (worse)	2 (3)	0 (0)	3 (4)	1 (1)	2 (4)	1 (2)	3 (7)	2 (5)
Total no. of eyes	74	76	68	72	57	53	46	42
Mean change (letters)	−3	−1	−6	−3	−5	−2	−4	−3
P	0.29		0.36		0.38		0.78	
95% confidence interval for difference in mean change (treated minus untreated)	−5.0 to 1.5		−6.9 to 2.5		−10.3 to 4.0		−10.6 to 8.0	

years of age, and showed both a cystoid pattern of macular edema and disc staining angiographically. This subgroup, however, is too small for a statistically valid comparison of treated and untreated eyes.

Macular Edema Results

Treatment significantly reduced the amount of macular edema measured by the Reading Center on the fluorescein angiogram. At the 12-month annual visit, no measurable macular edema was present in 21 (31%) of 68 treated eyes, whereas all of the 72 untreated eyes showed some macular edema ($P < 0.0001$). The effect of treatment was comparable in the two duration groups. In eyes with CVO of less than 1 year, only 13 (42%) of 31 treated eyes still had measurable macular edema present at the 24-month visit compared with 29(94%) of 31 untreated eyes ($P < 0.0001$). In eyes with CVO of 1 year or more, 11 (42%) of 26 treated eyes had measurable macular edema at the 24-month visit compared with 21 (95%) of 22 untreated eyes ($P < 0.0001$). Table 7 shows the disc areas of macular edema for treated and untreated patients at baseline and at each annual follow-up visit. The effect of treatment on macular edema was present in both older and younger patients.

The Reading Center also evaluated macular edema qualitatively on follow-up angiograms by comparing the intensity of leakage with the baseline angiogram. Of the 69 patients with an angiogram at the first follow-up visit

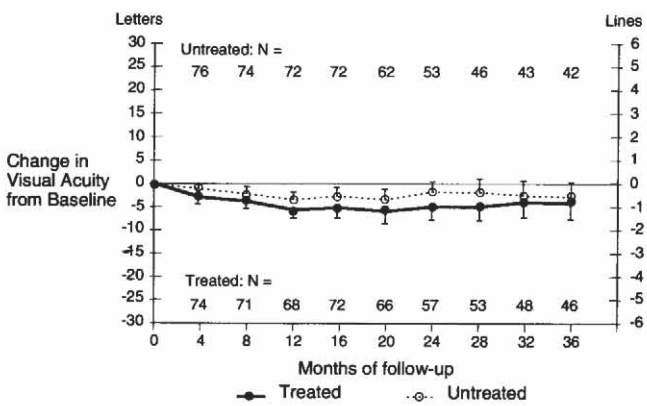

Figure 1. Mean change in visual acuity score from baseline at each follow-up visit by treatment allocation. Bars = one standard error of the mean; horizontal line = no change in visual acuity score.

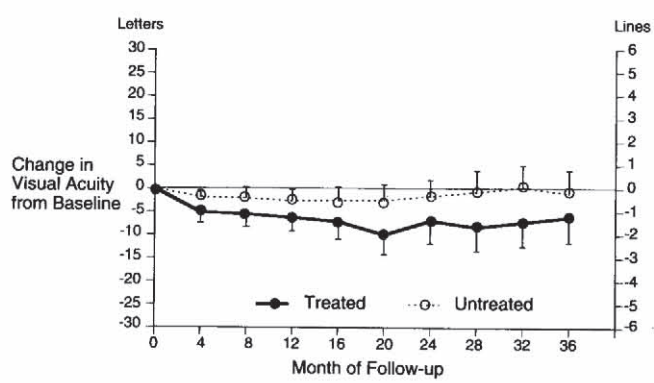

Figure 2. Mean change in visual acuity score from baseline at each follow-up visit by treatment allocation for subjects with central vein occlusion of less than 1 year. Bars = one standard error of the mean; horizontal line = no change in visual acuity score.

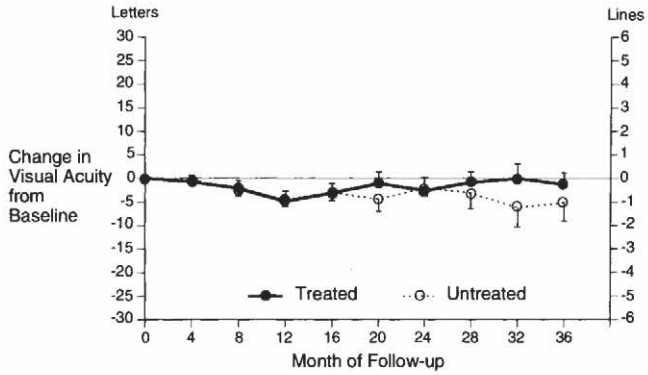

Figure 3. Mean change in visual acuity score from baseline at each follow-up visit by treatment allocation for subjects with central vein occlusion of 1 year or more. Bars = one standard error of the mean; horizontal line = no change in visual acuity score.

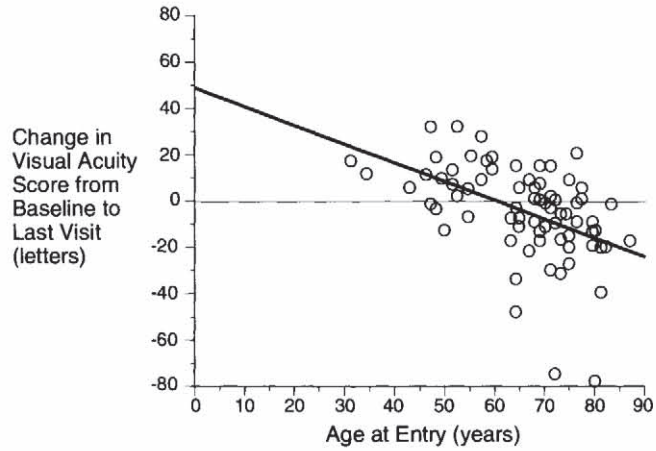

Figure 4. Change in visual acuity score from baseline to last visit by age at entry for treated eyes. Horizontal line = no change in visual acuity score; thick line = least-squares regression line.

(4-month visit), 33 (48%) of the treated patients showed improvement, 28 (41%) had no change, and 8 (12%) were worse. Among the 67 untreated patients, 12 (18%) had improved, 44 (66%) showed no change, and 11 (16%) were worse ($P < 0.001$).

Discussion

This study was designed to test whether macular grid-pattern laser photocoagulation or no treatment results in better visual acuity in eyes with reduced vision associated with macular edema from CVO. No difference in visual level or degree of change was seen between treated and untreated eyes. Treatment had no effect on visual acuity in either patients with CVO of recent onset (<1 year) or in occlusions of longer duration, despite a reduction in macular edema.

It is not clear why our results differ from previous studies, which have reported that patients with macular edema due to other retinal vascular diseases benefit from photocoagulation of the involved region. The lack of benefit from treatment in our study could have been due to a number of factors, including differences in the pathophysiology of the disease under study, the treatment that was used, or other characteristics associated with the study population.

Central vein occlusion usually results in diffuse capillary leakage involving all of the macular area, unlike early background diabetic retinopathy or branch vein occlusion.[9] Schatz and Patz[10] reported the results of grid pattern photocoagulation in three patients with diabetes who had diffuse macular edema similar to CVO with good capillary perfusion. All three of these patients had angiographic improvement of macular edema, but no improvement in visual acuity. In branch vein occlusion, it is much less common than in CVO for vascular abnormalities to involve 360° of the parafoveal capillary net. Most eyes with macular edema due to branch vein occlusion have 90° or more of angiographically normal parafoveal capillaries. Also in branch vein occlusion, collateral channels typically develop temporal to the macula crossing the horizontal raphe. This may permit a greater normalization of venous circulation in the recovery phase, as opposed to CVO, where collateral channels develop at the optic nerve. The requirement that the macular edema involve the center of the fovea and the additional characteristic that the macular edema typically includes all four quadrants in the parafoveal region may adversely affect the recuperative processes in the macula. This would be distinctly different from both branch vein occlusion and the early stages of diabetic macular edema. Therefore, the treatment in the CVOS, although limited to the area up to but not within the foveal avascular zone, resulted in surrounding the fovea with 360° of grid laser therapy. In the ETDRS, eyes treated with focal treatment fared better than those eyes with diffuse edema, who required a grid pattern of treatment. In the Branch Vein Occlusion Study, grid laser therapy was applied to less than 360°, most commonly 180° or less.

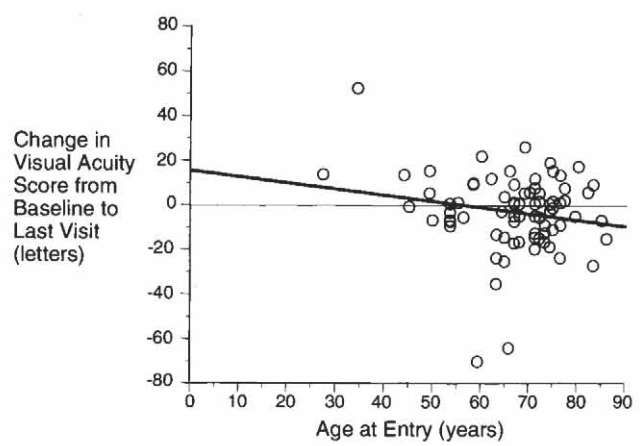

Figure 5. Change in visual acuity score from baseline to last visit by age at entry for untreated eyes. Horizontal line = no change in visual acuity score; thick line = least-squares regression line.

Table 7. Disc Areas of Macular Edema at Baseline and Each Annual Follow-up Visit

	Baseline		12 Mos		24 Mos		36 Mos	
	Treated	*Untreated*	*Treated*	*Untreated*	*Treated*	*Untreated*	*Treated*	*Untreated*
Disc areas of macular edema								
None	0 (0)	0 (0)	21 (31)	0 (0)	33 (58)	3 (6)	26 (57)	4 (10)
<2	2 (3)	2 (3)	10 (15)	4 (6)	2 (4)	5 (9)	1 (2)	3 (7)
2 to < 5	28 (36)	34 (44)	11 (16)	25 (35)	7 (12)	12 (23)	4 (9)	17 (40)
5+	47 (61)	41 (53)	15 (22)	35 (47)	5 (9)	23 (43)	4 (9)	13 (31)
Unavailable	0 (0)	1 (1)	11 (16)	8 (11)	10 (18)	10 (19)	11 (24)	5 (12)
Total no. of eyes	77	78	68	72	57	53	46	42
Median disc areas	5.5	5.0	1.5	5.0	0.0	5.0	0.0	3.0
P	0.73		<0.0001		<0.0001		<0.0001	

Characteristics of the population under study may have interacted with the effect of treatment. In particular, 44% of the patients with CVOS were older than 70 years of age, whereas the ETDRS excluded patients in this age group, and only 32% of patients in the Branch Vein Occlusion Study were older than 69 years of age. Only 15% of the patients in the ETDRS had visual acuity of 20/40 or worse at the time of entry. The CVOS required that visual acuity be 20/50 or worse for eligibility.

It is clear from the study results that grid laser photocoagulation promptly lessens macular edema angiographically. However, this angiographic improvement was not accompanied by an improvement in visual acuity. It is not clear why the reduction in angiographic evidence of macular edema did not result in better visual acuity in treated eyes. Irreparable damage to photoreceptors in the patients in the CVOS could be one reason. Such damage could be associated with the age of the patient, the severity of the subfoveal edema, or perhaps due to macular hemorrhage. Although hemorrhage involving the fovea was an exclusion criterion for entry into the study, once the hemorrhage cleared, such eyes could be determined eligible for the study. The parafoveal capillary circulation was carefully studied with fluorescein angiography, and eyes with capillary nonperfusion in the parafoveal region were excluded, but it is possible that eyes with less obvious inner retinal damage due to ischemia may have been included.

Overall, visual acuity results in the CVOS were not different for treated and control eyes. Therefore, we do not recommend grid pattern argon laser photocoagulation for macular edema due to CVO, based on the CVOS eligibility and treatment protocols. While there was a suggestion of possible benefit in the youngest patients, there were not enough patients younger than 60 years of age to differentiate this group sufficiently from the entire study group.

This is the first clinical research study of macular edema that has suggested a different response of older and younger patients to retinal laser photocoagulation. Future research is needed to verify the interaction of age and effects of treatment as well as describe aging changes in the retina.

Appendix

Study Group

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